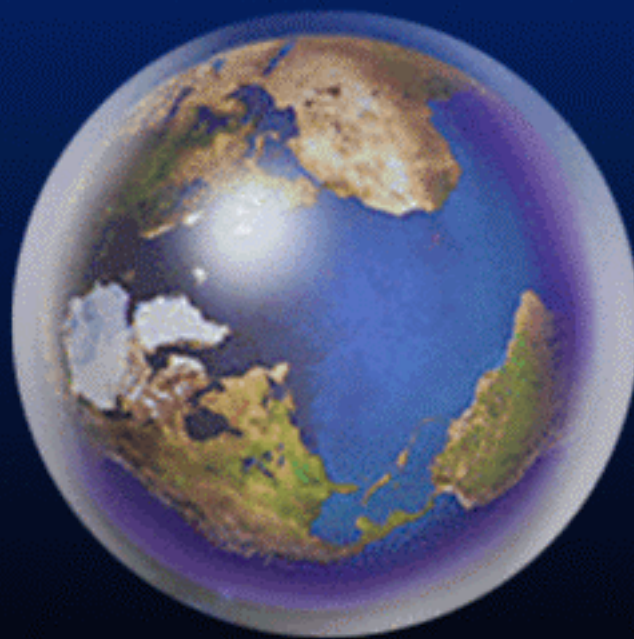


# NIAID: Planning for the 21st Century

*The National Institute of Allergy and Infectious Diseases  
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## EXECUTIVE SUMMARY

### Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) is the component of the National Institutes of Health (NIH) charged with conducting and supporting research on diseases of the immune system and infectious diseases. With a FY 2000 budget of over \$1.8 billion, NIAID is the third largest institute at NIH. During the past 15 years, three factors have prompted NIAID to grow significantly. First, the emergence of HIV/AIDS in the early 1980s shattered the notion that successful new vaccines and therapies had brought an end to infectious diseases. Second, results from basic research are now driving new approaches to solving clinical and public health problems. Third, is the realization that infectious diseases will continue to emerge unpredictably and at times explosively.

Today, there are more research avenues to invest in and opportunities to capitalize on than there were even five years ago. Consequently, planning has become a more critical element of the Institute's day-to-day operation. The need to prioritize opportunities to maximize potential advances is among the primary motivations driving our strategic plan. This draft plan also stems from the 1998 Institute of Medicine Report (IOM), *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*, which recommended that the NIH Director receive a forward-looking strategic plan, developed with public input, from each Institute and Center (IC). Because unforeseeable circumstances may shift the Institute's priorities, the plan is necessarily a dynamic document that will require reexamination over time.

NIAID's stewardship of this mission is driven by two convictions: strong commitment to basic research; and the understanding that the fields of immunology, microbiology, and infectious disease are related and complementary. Although the plan framework centers on four cornerstones - immune-mediated diseases (and immune tolerance), AIDS, emerging infectious diseases, and vaccines - considerable synergy exists within that framework.

#### **The NIAID Mission**

The NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives.

## **Planning and Priority Setting**

NIAID planning and priority setting occurs in a larger programmatic and resource allocation context. This context includes areas of emphasis determined by Congress, the Department, and NIH, a highly refined peer review process, the annual congressional appropriation, and other factors. Within that framework, NIAID supports both extramural and intramural research.

NIAID supports extramural studies initiated by individual investigators as well as those solicited by the Institute to address specific scientific opportunities, fill scientific gaps and respond to insufficiently met public health needs. To ensure scientific quality and public health merit, all extramural research applications undergo an extensive, two-tiered review process. At the first tier, scientific review groups judge applications. At the second tier, the National Advisory Allergy and Infectious Disease (NAAID) Council gives final approval to fund. The quality and merit of intramural research is assured through the laboratory review process. Support of intramural laboratory projects is based on budget resources, the outcome of review by the Board of Scientific Counselors, the relevance of the work to NIH and NIAID areas of emphasis, and other considerations, such as congressional mandates.

## **Public Input**

Public input is achieved in many ways. Representatives of voluntary health organizations and individuals based in health care are active on the NAAID Council. Also, NIAID's Executive Secretariat in the Office of Policy Analysis and its Office of Communications and Public Liaison establish and maintain strong links between the Institute and the public. These units respond to public inquiries, communicate NIAID news to the public, and funnel public concerns to appropriate NIAID divisions. Moreover, lay organizations actively participate in NIAID planning meetings. For example:

- The Directors of NIAID and the divisions frequently meet with lay organizations.
- On behalf of NIH, the Division of Allergy, Immunology, and Transplantation (DAIT) staffs the Coordinating Committee for Autoimmune Disease Research of which the *Ad Hoc* Coalition for Autoimmune Patient Groups is a member.
- PARA (patient advocates for Crohn's/*Mycobacterium paratuberculosis*) attended a workshop held, in part, to decide whether controlled antibiotic treatment trials are needed.
- Representatives of two patient advocacy groups are on the Advisory Panel for Clinical Studies in Chronic Lyme Disease and have made presentations to that group.
- The Division of AIDS (DAIDS) has been at the forefront in involving the community in all aspects of the research process. Community representatives sit on the AIDS Research Advisory Committee, which provides broad oversight and input and advises the Director on programmatic plans and priorities. Each of the prevention, vaccine, therapeutic, and epidemiological research networks supported by DAIDS has a national and/or local

Community Advisory Board (CAB). CABs are comprised of representatives from the volunteer research populations, such as: the parents of children with AIDS, individuals infected with HIV, and people at high risk for contracting HIV. The National CABs work with network leadership to develop a scientific agenda and set priorities. At the local level, CABs work with principal investigators to exchange information with the broader community and to assist with recruitment and retention of research subjects.

### **Development of the Draft Strategic Plan**

Strategic plan development began in January 1999 with division staff outlining recommendations from the range of planning and consultative events NIAID has participated in and sponsored in recent years. The Institute developed a strategic planning framework organized around four cornerstones, or broad areas, that encompass the NIAID research portfolio - immune-mediated diseases, AIDS, emerging infectious diseases, and vaccines. In July, the Institute convened a Strategic Planning Task Force made up of scientist and non-scientist members and comprising a panel for each cornerstone. The panels deliberated the priority areas and suggested revisions to the draft plan. The next iteration of the plan was later discussed during the September 1999 NAAID Council meeting. Following further revisions, for the month of November, the document was posted on the World Wide Web for public comment. This final draft, which reflects those comments, is being submitted to the Director, NIH, and will be discussed at the NAAID Council meeting in February 2000.

### **Scientific Opportunity**

Years of investment in basic research have generated remarkable opportunities to understand immune-mediated and infectious diseases. As biomedical research moves into the post-genomic era, DNA technologies are profoundly altering the health research landscape, including the study of immunology and infectious diseases. Those technologies and others are revolutionizing approaches to understanding pathogenesis, microbial physiology, and epidemiology of infectious diseases; radically advancing the understanding of immune activation and regulation; uncovering the genetic bases of disease susceptibility; and accelerating the development of new diagnostic, treatment, and intervention strategies.

Recent advances in computer modeling, x-ray crystallography, combinatorial chemistry, and robotics are being harnessed for rational drug design and high-throughput drug screening. These advances will provide faster and cheaper drug discovery, more precise and effective pharmaceuticals, and new drugs for diseases that have eluded previous treatment solutions.

Basic research has opened remarkable opportunities in other areas of immunology and infectious disease research. One of the most exciting, selectively blocking the immune response, might be used to treat many immune-mediated diseases. In addition, this approach may help achieve long-term, durable graft survival after transplantation.

## Public Health Need

### The Impact of Immunologic Diseases

Immunologic diseases – asthma and allergy, primary immunodeficiencies, and autoimmune diseases – afflict millions of Americans and result in considerable illness, death, and medical costs. Also, transplant rejection, caused by the normal response of a healthy immune system, remains a challenge in those instances where new organs or tissues are a patient's only hope.

- *Allergic Diseases and Asthma.* Allergies and asthma are major causes of illness and disability in the United States. More than 50 million Americans (1 out of every 5) suffer from allergies and/or asthma. Although asthma is a disease with low mortality, its economic costs are enormous with an estimated cost in the United States in 1996 of \$14 billion.
- *Autoimmune Diseases.* Autoimmune diseases are illnesses in which the immune system attacks the body's own tissues. Examples include diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. While many autoimmune diseases are rare, collectively these diseases afflict millions of people in the U.S. and a disproportionate number of women. The chronic nature of the diseases leads to high medical costs.
  - *Insulin-Dependent Diabetes Mellitus.* Also called Type 1 diabetes, this disease is caused by immune destruction of the pancreatic cells responsible for the production of insulin.
  - *Systemic Lupus Erythematosus (SLE).* SLE damages multiple tissues and organs. Muscles, skin, joints, and kidney, as well as the brain and nerves, may be affected.
  - *Rheumatoid Arthritis (RA).* RA usually begins as pain, swelling and tenderness of the small joints of the hands and feet. The mechanisms that trigger the inflammatory process that may cause destruction and deformity of the affected joints are not completely understood.
  - *Multiple Sclerosis (MS).* A chronic, inflammatory disease of the central nervous system, MS is the second most likely cause of more than 30 percent limitation in physical and outdoor activities. The disease frequently results in permanent disability.
  - *Graft Rejection.* For many victims of kidney failure, diabetes, leukemia, heart and liver disease, the ultimate treatment must be transplantation of an organ or tissue. Yet, often transplants fail. Graft rejection is second only to organ shortage as an impediment to long-term transplantation success.

People with immunologic diseases, and those taking immunosuppressive drugs to enhance graft acceptance, carry not only the burden of the primary illness but, because of their compromised immune systems, they also are at high-risk for infections.

## The Impact of Infectious Diseases

Infectious diseases are the second largest cause of death worldwide. The economic impact of infectious diseases is also great, with an estimated annual cost in excess of \$120 billion.

- *Acquired Immunodeficiency Disease (AIDS)*. In the United States, an estimated 271,000 people are living with HIV and the rate of new HIV infections, approximately 40,000 per year, continues at an unacceptably high level. Effective, low-cost tools of HIV prevention, such as a vaccine, are needed urgently to bring the HIV epidemic under control.
- *Tuberculosis (TB)*. TB is the eight leading cause of death worldwide. One-third of the world's population has latent TB, constituting a huge reservoir from which active TB can surface. Moreover, multi-drug resistant TB is an increasing problem.
- *Malaria*. Malaria has been undergoing a global resurgence in recent years with 275 million cases occurring annually, and a death toll estimated at 1.1 million.
- *Influenza*. Pneumonia and influenza are the sixth leading cause of death in the U.S. killing 10,000 to 40,000 people in an average flu season. Since 1918, at least three major influenza pandemics have occurred. The worst of which, the pandemic of 1918-1919, caused about 500,000 deaths in the U.S. and 20,000,000 worldwide.
- *Hepatitis*. Hepatitis (liver inflammation) can be caused by a variety of viruses. The most common include hepatitis A virus (HAV), which causes acute liver inflammation and is generally transmitted from contaminated food or water; hepatitis B virus (HBV), which is an easily transmitted, bloodborne disease that leads to chronic infections, especially in newborn children infected at birth (chronic HBV infection is also a leading cause of liver cancer); and hepatitis C virus (HCV), which also is bloodborne and has infected almost 4 million people in the United States (2.7 million chronically infected). Although HCV may not cause symptoms for 20 or more years, about 85 percent of infected individuals eventually develop chronic liver disease, 20 percent develop cirrhosis, and a smaller percent liver cancer. About 9,000 people die annually from HCV. A good vaccine candidate is still needed.
- *Emerging Infections*. There are numerous emerging infectious agents among the viruses, bacteria, protozoa, and fungi that make up the microbial world. Because the frequency of world travel makes the United States part of a global community, diseases that emerge in foreign countries are also health threats in the United States.
- *Bioterrorism*. Terrorist incidents involving biological agents are uniquely complicated because of the large number of potential agents, their long incubation periods and possible delayed onset of disease, as well as their potential for communicable spread. Unlike naturally occurring pathogens, agents used by bioterrorists may be genetically engineered to resist current therapies and evade vaccine-induced immunity.

## **Accomplishments**

The outstanding contributions of NIAID-supported investigators extend from basic discoveries in microbiology and immunology to the development of vaccines, drugs, and diagnostic tools.

### **Immune-Mediated Diseases**

NIAID investment in research on processes of immune activation and regulation, and on the genetic basis of disease susceptibility, have elevated our conceptual understanding of the immune system.

Some key discoveries in basic immunology research include: discovering mechanisms of antibody diversity; defining humoral and cell-mediated immunity; discovering immune response genes and the genetic bases for many primary immunodeficiency disorders; and developing ways to treat them.

Research on allergies and asthma has defined the role of inflammation and viral infections in asthma and has delineated the molecular mechanisms of the allergic response, including the role of IgE antibodies, the characterization of the IgE receptor, and the discovery of leukotrienes.

New immunosuppressive therapies have substantially improved kidney transplants and allowed transplantation of a variety of other organs. Better understanding and characterizing of major histocompatibility complex (MHC) genes has substantially improved donor-recipient matches, and vast improvements have been made in tolerizing bone marrow transplants to prevent graft-vs.-host disease.

Advances in autoimmunity research include discovering the role of MHC and other genes in diseases susceptibility and understanding the role of regulatory T-cell networks in controlling self-reactive cells. Several treatments to modulate the immune response have been developed, including cytokines and anti-cytokines, and the combination of glucocorticoids with cyclophosphamide.

#### **A Story of Discovery: Transplant Tolerance**

In the past decade, discoveries made by NIAID-supported scientists about mechanisms that activate and regulate the immune response have yielded a new approach to preventing transplant rejection. Rather than suppressing the entire immune system, a targeted strategy has been designed to induce tolerance (the lack of an immune response) by turning off the specific immune cells that attack the transplant. Although more research is needed to develop therapies, NIAID-supported research on immune tolerance is contributing to the eventual development of ways to improve transplant success and of new treatments for a wide range of immunologic disorders.



## **Acquired Immunodeficiency Syndrome**

In the United States and other parts of the industrialized world, the number of new AIDS cases and AIDS-related deaths has dropped dramatically. This has largely been the result of powerful new antiviral drug treatments that have prolonged and improved the quality of life for many HIV-infected people. NIAID-supported basic research identified the HIV protease enzyme as a target for antiviral drugs, which led to the development of very potent protease inhibitors and demonstrated the effectiveness of triple-drug treatments (combinations of protease inhibitors and reverse transcriptase inhibitors), often called "highly active antiretroviral therapy," or HAART, over one- or two-drug treatments. NIAID research also led to better ways to prevent perinatal transmission of HIV, first by treating infected pregnant women and their infants with AZT, and more recently, by a single dose each to mother and child of the highly cost-effective drug nevirapine.

### **A Story of Discovery: Protease Inhibitors - A New Class of Anti-HIV Drugs**

Institute-supported basic research was pivotal to the discovery and definition of the importance of the HIV protease enzyme, which is used by the virus to produce infectious HIV particles. Institute-supported scientists also helped determine the precise three-dimensional structure of HIV protease, a crucial step in designing drugs that block the action of the enzyme. Additionally, NIAID supported researchers helped drug-screening efforts by developing simple, rapid tests to measure the inhibition of protease activity. These NIAID accomplishments set the stage for the Institute's successful collaboration with the pharmaceutical industry in developing the new class of anti-HIV drugs known as protease inhibitors.

### **A Story of Discovery: Nevirapine-A Global Weapon to Battle Maternal-to-Infant HIV Transmission**

HIV/AIDS is a truly global health threat affecting all nations and all population subgroups. Now, for the first time, there is a potent and inexpensive means of reducing the incidence of HIV/AIDS infection in one of the most vulnerable populations of all--newborn babies of HIV-infected mothers. In a collaborative effort involving research scientists at the Johns Hopkins University in Baltimore, the University of Washington in Seattle, and the Makerere University in Kampala, Uganda, investigators supported by NIAID's HIV Prevention Trials Network (HIVNET) have achieved a stunning breakthrough--a practical means of significantly reducing the rate of maternal-to-infant HIV transmission. A single dose of nevirapine, to mother and child, reduced the rate of maternal-infant transmission by half when compared to a similar short course of zidovudine (AZT). In developing countries, this approach may prevent 300,000 to 400,000 newborns from suffering the effects of HIV infection. The nevirapine regimen also has the potential to provide last-minute HIV prevention for the babies of pregnant women who do not know their HIV status until they are admitted to a health care facility for delivery. Nevirapine has significant implications for HIV-infected mothers in the United States as well, especially in minority populations that have been particularly stricken by the AIDS epidemic and that have limited access to prenatal care or to health care in general.

## Emerging Infectious Diseases

Research endeavors to understand microbes, how they cause disease, and how they develop drug resistance and to use that knowledge to develop new diagnostic tools and interventions. Toward that goal, NIAID research has identified infectious agents for several human diseases, including Lyme disease, bronchopneumonia, hemorrhagic fevers, and diarrheal illness. The sequenced genomes of *Treponema pallidum* (syphilis), *Escherichia coli* strain K 12, *Chlamydia trachomatis*, *Plasmodium falciparum* chromosome 2 (malaria), and *Mycobacterium tuberculosis* will lead to more specific targets for diagnosis and antibiotic and vaccine development. Finally, NIAID-supported clinical trials have led to new therapies for influenza, Lyme disease, hantavirus pulmonary syndrome, and fungal infections.

## Vaccine Development

Development of new vaccines provides safe, cost-effective and efficient means of preventing disease, illness, disability, and death from infectious diseases. Just four (hepatitis B, conjugate *Haemophilus influenzae* type B, pneumococcus, and acellular pertussis) of the many vaccines developed recently by NIAID and its collaborators have the potential to save million lives annually. Other vaccines developed with substantial support from NIAID include hepatitis A, adenovirus, typhoid, meningococcus, and, influenza.

### **A Story of Discovery: *Haemophilus Influenzae* Type b (Hib) Vaccine**

As recently as 20 years ago, children worldwide frequently died of bacterial meningitis and 1 in 200 children in the United States contracted *Haemophilus influenzae* type b (Hib), the primary cause of bacterial meningitis. A quarter of those who survived had brain damage or hearing loss. Today, thanks to the Hib vaccine developed by NIAID-supported researchers, Hib is a rarity. Introduced in 1985, the Hib vaccine boosted immunity in infants (who have a poorly developed immune system) by linking the bacterium's polysaccharide coat to a protein (thus creating a conjugate vaccine). The spinoffs of this breakthrough still reverberate. The conjugate vaccine technology developed for Hib, now a proven approach to the develop of vaccines for the very young, is being applied to other diseases as well.

## **Cornerstones of the Strategic Plan**

### **Immune-Mediated Diseases**

Despite considerable remaining gaps in our knowledge, we are steadily increasing our understanding of the body's immune system. As we enter the next century, these advances provide a solid foundation for translating (converting) basic research into clinical applications. NIAID's strategic plan for immune-mediated diseases focuses research efforts in several areas, including: 1) developing new tolerogenic and immunomodulatory approaches to treat autoimmune diseases, asthma and

allergic diseases, and graft rejection in solid organ, tissue, and cell transplantation; 2) developing effective vaccines to prevent and treat immune-mediated diseases; 3) applying emerging technologies to advance fundamental understanding of immunologic principles and to develop better diagnostic tools, improved patient monitoring techniques, surrogate markers of disease activity, and more effective therapies; and 4) continuing long-term support of fundamental discoveries of immune regulation that may ultimately be translated into practical applications for treating and preventing a broad range of diseases.

## **BASIC IMMUNOLOGY**

Continued investment in basic immunology research is a fundamental strategy to help ensure future progress in vaccine development, as well as in the diagnosis, prevention, and treatment of allergic and immunologic diseases.

### **Goals**

- Standardize measurement of immune function at the cellular, biochemical, and molecular levels to facilitate understanding disease pathophysiology.
- Maintain a pipeline of fundamental discoveries of immune regulation for translation into practical applications for vaccines and a broad range of immune-mediated diseases.
- Exploit immunologic principles to stimulate residual immune function in immunosuppressed individuals.
- Support underserved areas of research, such as: 1) immune regulation at specialized anatomical sites; 2) immune regulation at different stages of human development; and 3) the role of the innate immune system in regulating adaptive immunity.
- Integrate immune research with other research disciplines, such as cellular and molecular biology, tumor biology, neurology, genomics, proteomics, and bioinformatics.

### [Opportunities and Plans](#)

## **IMMUNE TOLERANCE**

The successful induction of immune tolerance is a major goal for the treatment of many immune-mediated disorders, including autoimmune diseases, such as rheumatoid arthritis, Type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and graft rejection of transplanted organs, tissues, and cells. This ability to maintain a tolerant state will be equally important for preventing immune unresponsiveness to vaccines against tumors and infectious diseases.

## **Goals**

- Develop new tolerogenic approaches for the treatment of many immune-mediated diseases.
- Expand knowledge of the molecular basis for tolerance induction.

## [Opportunities and Plans](#)

### **TRANSPLANTATION**

Transplantation is the therapy of choice for treating many diseases resulting in organ failure. NIAID's long-term investment in molecular immunology has created extraordinary opportunities to accelerate the clinical application of tolerance induction therapies to achieve long-term, durable, graft survival while maintaining immune competence.

## **Goal**

- Improve both short- and long-term clinical outcomes by developing new therapeutic approaches to prevent graft rejection and by continuing the expansion of our knowledge of the mechanisms of immune rejection.

## [Opportunities and Plans](#)

### **ASTHMA AND ALLERGIC DISEASES**

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States and disproportionately affect disadvantaged, inner-city populations. Recent scientific advances in understanding the genetic basis and immunologic mechanisms of asthma and allergic diseases provide new opportunities for prevention and treatment.

## **Goals**

- Develop more effective treatments for asthma and allergic diseases.
- Develop interventions to disease onset.

## [Opportunities and Plans](#)

### **AUTOIMMUNE DISEASES**

Millions of individuals are affected by autoimmune diseases, but women are affected disproportionately. Alleviating or preventing the debilitating effects of autoimmune disease requires a broad strategy focusing on disease induction, remission, relapse; organ damage; genetic susceptibility; the role of infectious and environmental factors; new therapeutic approaches; and eventually designing interventions, such as vaccines, to prevent disease onset.

## **Goals**

- Identify specific autoantigens in autoimmune diseases.
- prevent the development of and effectively intervene in ongoing disease.

## [Opportunities and Plans](#)

### **GENETICALLY DETERMINED IMMUNODEFICIENCY DISEASES**

Enormous progress has been made in understanding the molecular bases of a growing number of genetically determined immunodeficiency diseases owing to the gene-discovery tools provided by the Human Genome Project. Still, many disease mechanisms remain to be identified and characterized at the molecular level. Knowledge about the molecular basis of primary immunodeficiency disease is important for understanding the pathogenesis of autoimmune and malignant diseases, which occur with increased frequency among patients with primary immunodeficiencies.

## **Goals**

- Identify gene mutations that cause defects in the immune response leading to disease.
- Define the physiological roles of the proteins encoded by such genes.
- Develop effective therapies, including gene therapy, for immunodeficiency disorders.

## [Opportunities and Plans](#)

### **IMMUNOLOGIC BASIS OF EFFECTIVE HUMAN VACCINES**

Understanding human immunity is increasingly important for rational design and development of vaccines against major diseases, in which natural immune responses fail and there is little empirical guidance for vaccine development. Support for increased collaborations between basic immunologists and clinical vaccine researchers is critically important.

## **Goal**

- Facilitate the rational design and development of vaccines by supporting research aimed at understanding fundamental principles of protective immunity in humans.

## [Opportunities and Plans](#)

## **INFECTIOUS ETIOLOGIES OF CHRONIC IMMUNE-MEDIATED DISEASES**

Infectious agents are major contributing or causative factors in the development of many chronic diseases. Mounting evidence indicts them as underlying causes of cancer, coronary artery disease, diabetes, multiple sclerosis, autism, and chronic lung diseases. Identification of infectious agents as causative factors in chronic disease will revolutionize clinical diagnosis and treatment of these debilitating conditions and provide unique opportunities to prevent many diseases through new vaccine development.

### **Goals**

- Develop cross-disciplinary programs with the capacity to identify infectious agents involved in the initiation and maintenance of human chronic diseases.
- Define mechanisms by which infectious agents and/or the immune response cause disease pathogenesis.

### [Opportunities and Plans](#)

## **Acquired Immunodeficiency Syndrome (AIDS)**

Since HIV was first identified in 1983, enormous progress has been made in understanding how the virus attacks the immune system to cause disease and in how to intervene therapeutically. NIAID-funded researchers have also made great strides in reducing mother-to-infant transmission of HIV. Twenty-seven different preventive vaccines have been evaluated, and efforts are under way to increase the number of new vaccine and microbicide candidates.

Still, research is needed to identify new strategies and tools to accelerate drug and vaccine discovery, to better understand immune reconstitution, and to determine the most promising drug candidates. Viral drug resistance remains a major obstacle to effective, long-term therapy. Finally, for HIV prevention efforts to have a global impact, effective, inexpensive, and easily administered regimens need to be developed, especially with regard to mother-infant transmission.

## **EPIDEMIOLOGY**

Epidemiologic research provides information that advances our understanding of the biology and clinical course of HIV infection. Comprehensive data and biological sample collections from individuals who are either at high risk for HIV infection or are already infected provide a complete picture of HIV infection and disease, and serve as a unique resource for investigations of immunologic, virologic, genetic, and other factors that may modulate the various stages of HIV disease.

## **Goal**

- Understand the changing pattern of HIV infection throughout the world, and the impact of therapeutic, vaccine, and other prevention-based interventions on survival and clinical outcome.

## [Opportunities and Plans](#)

### **PATHOGENESIS**

HIV pathogenesis research increases our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. Knowledge gained from these studies enhances the ability of researchers to create new agents and vaccines to combat HIV infection. Nonetheless, more information is needed about how the virus evades the immune system.

## **Goal**

- Understand how HIV causes disease.

## [Opportunities and Plans](#)

### **TREATMENT**

NIAID-sponsored therapeutics research has had a dramatic impact on the clinical management of HIV infection over the past decade. Recent studies have shown that highly active antiretroviral therapy (HAART) - regimens of at least three antiretroviral drugs, (i.e., reverse transcriptase inhibitors and usually at least one protease inhibitor) - is capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV morbidity and mortality in this country. Nonetheless, there is an ongoing, urgent need for new therapeutic agents to control HIV replication and boost, rebuild, and/or replace immunity lost in HIV infection.

## **Goal**

- Extend the gains in survival and quality of life achieved by current therapy by minimizing the adverse effects of long-term treatment and, ultimately, to cure HIV infection.

## [Opportunities and Plans](#)

## **HIV VACCINES**

The discovery and development of a vaccine that protects against HIV infection is one of the highest priorities of the NIH AIDS research program. To accelerate identification of effective vaccine candidates, future studies will need to address the significance of latently infected cells, immune responses induced by current vaccine candidates, and the impact of HIV and HLA diversity. Because the majority of new HIV infections are occurring in the developing world, strong international collaborations will need to be formed and ethical issues addressed in order to conduct efficacy studies in developing countries.

### **Goal**

- Identify and develop safe, effective vaccines to protect people from HIV infection and disease.

### [Opportunities and Plans](#)

## **NON-VACCINE PREVENTION STRATEGIES**

Control of the AIDS epidemic will probably require a combination of prevention strategies to protect against HIV infection, even in the presence of an efficacious vaccine. Such strategies include methods to interrupt mother-to-infant transmission of HIV; biomedical approaches, such as topical microbicides and the treatment of sexually transmitted diseases (STDs); and behavioral interventions.

### **Goal**

- Identify safe, efficacious, cost-effective non-vaccine interventions to prevent the transmission of HIV.

### [Opportunities and Plans](#)

## **Emerging Infectious Diseases and Global Health**

Despite remarkable advances in medical research and treatments during the 20th century, infectious diseases remain among the leading causes of death worldwide for three reasons: 1) emergence of new infectious diseases; 2) re-emergence of old infectious diseases; and 3) persistence of intractable infectious diseases. Many logistical and scientific challenges stand in the way of better prevention, treatment, and control strategies for emerging diseases and those infectious diseases that primarily impact the developing world. Addressing these challenges will require collaboration among the biomedical industry, government agencies, international organizations, and private foundations.



## **MICROBIOLOGY AND VECTOR (TRANSMISSION PATHWAY) BIOLOGY**

Expanded studies in microbiology and infectious disease ecology will improve prediction and prevention. Research in specialized fields such as molecular biology, genetics, cell biology, population and evolutionary biology, mathematical modeling, computer science, and remote sensing technology is essential to this effort.

### **Goal**

- Enhance our ability to predict and prevent conditions that lead to human disease by understanding the complex dynamic between and among pathogens, potential host carriers, and the environment.

### [Opportunities and Plans](#)

## **DIAGNOSIS AND DETECTION**

Rapid, sensitive methods for pathogen identification and disease diagnosis, determination of the drug sensitivity of microbes, and determination of the pesticide sensitivity of arthropod vectors would significantly increase the quality of patient care and simplify infectious disease control and surveillance programs. New research suggests that many "noncommunicable" diseases are caused or exacerbated by infectious agents. The potential health burden of these diseases warrants more extensive analysis of the contributions of infectious agents to chronic diseases.

### **Goal**

- Strengthen our ability to diagnose human infectious diseases and detect pathogens in the environment.

### [Opportunities and Plans](#)

## **TREATMENT**

The goal of treatment research is to identify targets of vulnerability during the complex processes of colonization, replication, and eventual transmission to new hosts. Recent advances in structural biology, computer modeling, crystallography, combinatorial chemistry in drug design, and robotic technology for high-throughput screening must be harnessed to identify and produce candidate compounds for therapeutic use. Design of therapies against unknown pathogens, whether naturally emerging or the result of bioengineering, poses a special challenge and emphasizes the need for developing better broad-spectrum antimicrobial agents.

### **Emerging Diseases Research Goals**

- Strengthen basic and applied research on the multiple host, pathogen, and environmental factors that influence disease emergence.
- Support the development of diagnostics, vaccines, and therapies necessary to detect and control infectious diseases.
- Maintain the national and international scientific expertise required to respond to health threats.

## **Goal**

- Develop new and improved methods for treating illness, controlling outbreaks, and preventing epidemics.

## **Opportunities and Plans**

### **DRUG AND INSECTICIDE RESISTANCE**

Development of resistance is fueled by increased and/or inappropriate drug use and amplified by person-to-person or common-source transmission in crowded settings such as hospitals. Agricultural practices that include extensive use of antibiotics in livestock and pesticides on crops are adding selective pressure on microbes.

## **Goal**

- Develop new strategies to control diseases that are re-emerging due to drug or insecticide resistance.

## **Opportunities and Plans**

### **GLOBAL HEALTH**

Improving our global ability to combat infectious diseases that are resistant to current control strategies presents many unique research challenges. Basic research is needed to understand how pathogens evade normal host defenses, and epidemiological and field-based research is needed to understand the natural history of disease.

## **Goal**

- Identify better control strategies for intractable infectious diseases that continue to challenge global health.

## **Opportunities and Plans**

## **Vaccines**

Widespread use of vaccines to prevent infectious diseases is one of the greatest public health achievements of this century. Basic science and applied research, fueled by NIAID investments, are creating unprecedented opportunities to expand vaccine discovery and development within the next five years. NIAID plans for vaccine research is focused in four areas: 1) vaccine discovery, design, and development; 2) development of vaccines against pathogens associated with emerging and potentially re-emerging global health problems; 3) overcoming obstacles to development of vaccines against pathogens of high public health importance that have eluded preventive intervention; and 4) vaccine discovery and development in newly identified areas of need.

## **VACCINE DISCOVERY, DESIGN, AND DEVELOPMENT**

Understanding human immunity, analyzing the molecular dynamics of binding complexes during host/pathogen interactions, and utilizing the pathogen and host gene expression profiles will be increasingly important for the discovery, design, and development of future vaccines. Translation from discovery to development will require early recognition of practical needs, such as single dose, temperature-stable formulations delivered by novel routes (skin, nose).

### **Goals**

- Facilitate the discovery, design, and development of vaccines through expanded knowledge of the molecular and immunologic interplay between host and pathogen.
- Foster collaborative interactions among various disciplines to accelerate progress in vaccine discovery, design, and development.

### [Opportunities and Plans](#)

## **PATHOGENS ASSOCIATED WITH EMERGING AND RE-EMERGING GLOBAL HEALTH PROBLEMS**

Pathogen emergence and re-emergence are influenced by a variety of factors. Despite the breadth of potential needs, the basic research requirements associated with the development of vaccines against emerging infections is similar.

### **Goal**

- Support broad and stable research programs that will rapidly expand vaccine development for emerging and re-emerging pathogens associated with global health problems.

### [Opportunities and Plans](#)

## **OVERCOMING OBSTACLES TO VACCINES FOR PATHOGENS OF HIGH PUBLIC HEALTH IMPORTANCE**

Scientific, technical, theoretical, and political obstacles have hampered the development of several vaccines against diseases of high public health importance. Expanding knowledge of the host-pathogen relationship and the genetic organization of malaria and tuberculosis has resulted in renewed enthusiasm that these diseases may be controlled by vaccines. In the United States, other equally important pathogens, previously intractable to vaccine development, have been identified for renewed efforts.

### **Goals**

- Re-address vaccine development strategies for diseases of greatest health importance using the expanded knowledge gained by novel technologies and microbial pathogenesis.

- Pursue alternative strategies and address existing barriers, such as modes of vaccine delivery, immunopotential, and reactivation, in diseases of high global health importance.
- Pursue programs in neglected areas of national and international needs.

### Opportunities and Plans

#### **NEWLY IDENTIFIED AREAS OF VACCINE NEED**

Expanding the scientific base for developing therapeutic vaccines for chronic diseases and opportunities to improve health through vaccines against non-traditional health targets are an important component of the NIAID plan. To be successful, scientific opportunity and public health need to merge in three areas: 1) management of chronic diseases of infectious and non-infectious origin; 2) control of autoimmune diseases through tolerogenic and non-tolerogenic approaches; and 3) special circumstances, such as the development of vaccines against potential bioterrorism agents.

#### **Goal**

- Explore opportunities for vaccine development in less traditional areas, including therapeutic vaccines for the management of chronic diseases; vaccines for the control of autoimmune diseases; and vaccines for special circumstances of public health concern, such as bioterrorism.

### Opportunities and Plans

## **Selected Crosscutting Elements**

Underpinning the four cornerstones of the strategic plan are crosscutting needs to develop new technologies, foster application of findings, train investigators, and to interrelate with the Institute's stakeholders.

#### **INFRASTRUCTURE FOR TECHNOLOGY DEVELOPMENT**

Many of the goals in this draft plan are based on new insights and approaches made possible by DNA sequence information and the capability to manipulate that information with complex computational systems. By revolutionizing approaches to pathogenesis, microbial physiology, and epidemiology of infectious diseases, and by radically advancing the understanding of immune activation and regulation, genomic research will markedly accelerate the development of new diagnostic, treatment, and prevention strategies. Other technologies, including computer-assisted means to visualize molecules, have had a profound impact on immunology and infectious disease research as well.

## **Goal**

- Establish the infrastructure to support the development and use of new technologies in immunology and microbiology.

## [Opportunities and Plans](#)

### **TRANSLATION OF RESEARCH**

The path from basic research to health care is a long one, involving many steps and considerable interaction with other organizations. To ensure that the benefits of basic research are realized, NIAID initiates research-planning activities, supports and conducts applied research, and undertakes various technology transfer efforts.

## **Goal**

- Facilitate the movement of fundamental discoveries toward the development of new and improved diagnostics, drugs, and vaccines.

## [Opportunities and Plans](#)

### **RESEARCH TRAINING AND CAREER DEVELOPMENT**

Intellectual talent propels the research enterprise and must be sustained not only to replace retiring investigators, but also to reflect the changing needs of science. In addition, NIAID is committed to help improve the representation of minorities in research.

## **Goal**

- Ensure that a sufficient number of talented investigators, including those from diverse backgrounds, enter immunology and infectious diseases research, and the subfields therein, so shortages of top scientists do not impede basic research or the translation of science advances into medical practice.

## [Opportunities and Plans](#)

### **OUTREACH**

The full benefit of NIAID research can be realized only when new knowledge is disseminated to not only other scientists, but also to health care providers and the public. Also, the interests and concerns of the public and other stakeholders must be integrated in the research planning process. NIAID is committed to executing a strong public liaison function in both respects.

## Goal

- Promote and sustain interaction with health care professionals and the public through proactive communication of research results, and genuine solicitation and serious consideration of input.

## Opportunities and Plans

### DIRECTOR'S FOREWORD



Anthony S. Fauci, M.D.  
Director  
National Institute of  
Allergy and Infectious  
Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) is the component of the National Institutes of Health (NIH) charged with conducting and supporting research on immunologic and infectious diseases. During the past 15 years, three factors have prompted NIAID to grow significantly. First, the emergence of HIV/AIDS in the early 1980s shattered the notion that successful new vaccines and therapies had brought an end to infectious diseases. Second, the Institute's historical commitment to basic research in immunology and microbiology paid major dividends with remarkable new insights into the immune system, immunologic disease, the immune response to infection, the physiology and genetics of infectious microbes, and the pathogenesis of infectious disease. Results from this basic research are now driving new approaches to solving clinical and public health problems--the heart of the Institute's mission. Third is the realization that infectious diseases will continue to emerge unpredictably and at times explosively.

New transportation modes enable local outbreaks of new infectious diseases to escalate rapidly into global problems. The last decade alone has witnessed several, such as the resurgence of cholera in the Americas after over a century, the emergence of hantavirus in the continental U.S., new influenza viruses, West Nile virus in New York City, and many other threats. In addition, the world now faces the menace of bioterrorism. These problems illustrate just a few of the tremendous challenges facing immunology and microbiology researchers.

Fortunately, these challenges arise at a time when technologies to approach them have never been more powerful. Ironically, these new technologies are creating a different challenge for the Institute. Today, there are more research avenues to invest in, and opportunities to capitalize on, than there were even five years ago. Consequently, planning has become a more critical element of the Institute's day-to-day operation. The need to prioritize opportunities to maximize potential advances is among the primary motivations driving our strategic plan.

This plan also stems from the 1998 Institute of Medicine Report (IOM), *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*, which recommended that the NIH Director receive a strategic plan from each Institute and Center (IC). In response, the NIH Director asked each IC to develop, with public input, a strategic plan with members of Congress and the public as its primary audiences.

As the capstone of an ongoing planning process, this document describes broad-based Institute priorities that will guide NIAID programs, policies, and initiatives through the next three to five years. Two major factors will influence execution of this plan. First is the impact of natural and logical areas of overlap among the four cornerstones of this plan on research progress.

These overlaps are considered advantageous because they reinforce a clear trend in science toward multidisciplinary research. Second, because unforeseeable circumstances may shift the Institute's priorities, the plan is necessarily a dynamic document that will require reexamination over time.



Anthony S. Fauci, M.D.

*Director*

*National Institute of Allergy & Infectious Diseases*

#### **THE NIAID DIRECTOR**

Anthony S. Fauci, M.D., became the Director of NIAID in November 1984. He received his medical degree from Cornell University Medical College in 1966, completed his internship and residency at Cornell Medical Center, and joined NIAID in 1968 as a clinical associate in the Laboratory of Clinical Investigation (LCI). In 1977, he was appointed Deputy Clinical Director of NIAID, and in 1980, he was appointed Chief of the Laboratory of Immunoregulation, a position he still holds.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He is an internationally renowned scientist and has pioneered the field of human immunoregulation by making a number of fundamental scientific observations that serve as the basis for current understanding of the regulation of human immune response. Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses, which leads to its susceptibility to deadly infections. He has also delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease, as well as for a vaccine to prevent HIV infection.

Dr. Fauci is a member of the National Academy of Sciences, the Institute of Medicine (Council Member), the American Academy of Arts and Sciences, as well as a number of other professional societies and editorial boards.

## INTRODUCTION

### THE NIAID MISSION

NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives.

NIAID's stewardship of its mission is driven by two convictions. The first relates to the paramount importance of strong research bases to address unknown, future health threats. The breadth and depth of our knowledge of immunology and microbiology, for example, has been central to the rapid development of powerful AIDS treatments. Sustaining strong research bases in these areas will be vital to controlling the next global health threat. It is also critical to continue progress across the broad front of unconquered infectious and immune-mediated diseases. Although space limitations prevent a complete discussion here, NIAID is resolved to conduct and support research to understand, treat, and prevent the full range of infectious and immunologic diseases, including sexually transmitted diseases (STDs), fungal infections, foodborne illnesses, and primary immunodeficiency diseases.

The second conviction is that the fields of immunology, microbiology, and infectious disease are related and complementary. Although the plan framework centers on four cornerstones - immune-mediated diseases and immune tolerance, AIDS, emerging infectious diseases, and vaccines - considerable synergy exists within that framework.

## NIAID OVERVIEW



NIAID is one of 25 Institutes and Centers (ICs) at the National Institutes of Health (NIH), which in turn is an agency within the U.S. Department of Health and Human Services (DHHS). With a FY 2000 budget of over \$1.8 billion, NIAID is the third largest institute at NIH.



NIAID receives advice on policy and program from the [National Advisory Allergy and Infectious Diseases \(NIAID\) Council](#), which also performs the second-level review of funding proposals. Mandated by law, the Council is a chartered advisory committee, comprised of both scientific and lay members, which meets three times a year.

## ORGANIZATION

[The Institute](#) is organized into five divisions. Approximately 11 percent of the budget supports NIAID's [Division of Intramural Research \(DIR\)](#), which is comprised of 15 laboratories and 4 branches that conduct basic and clinical research. Additional intramural research is conducted at the Dale and Betty Bumpers Vaccine Research Center in partnership with the National Cancer Institute. Approximately 85 percent of the NIAID budget supports extramural research through three divisions:



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## *NIAID: Planning for the 21<sup>st</sup> Century*

the [Division of AIDS \(DAIDS\)](#); the [Division of Allergy, Immunology and Transplantation \(DAIT\)](#); and the [Division of Microbiology and Infectious Diseases \(DMID\)](#). These divisions fund and administer extramural research in academic and industry laboratories in the United States and abroad. The [Division of Extramural Activities \(DEA\)](#) oversees policy and management for grants and contracts, including peer review of certain applications. DEA also manages the Office of Special Populations and Research Training. The five divisions are served by various administrative offices, including: Communications and Public Liaison; Clinical Research; Equal Employment; Financial Management; Human Resources; Policy Analysis; Technology Development; and Technology Information Systems. The divisions and offices report to the Office of the Director. In turn, the Director of NIAID reports to the Director of NIH.

### **RESEARCH MANAGEMENT**

Less than 4 percent of NIAID's budget funds research management and other support. NIAID is known for innovative approaches to application review and grants administration. The Institute was first to establish expedited review and award procedures and continues to lead the effort by awarding the majority of investigator-initiated R01 grants in six rather than nine months. Moreover, NIAID pioneered Internet-assisted review, which improves the quality of the peer review process, provides flexibility in how the review is conducted, and saves time for applicants, reviewers, and staff. In short, NIAID is strongly committed to maximizing the time and resources available for scientific investigation by streamlining grant administration and decreasing the time between application and award.

### **PARTNERSHIPS**

NIAID frequently coordinates and collaborates with other research organizations and groups working to improve health care. The Institute participates in NIH-wide initiatives, collaborates with sister agencies in DHHS and other federal departments, and works with international and non-governmental organizations. In addition, the Institute interacts with the private sector in a variety of ways that promote application of research findings in health care settings.

#### **Selected NIAID Partnerships**

- Dr. Fauci heads the Panel on Clinical Practices for Treatment of HIV Infection. The panel is responsible for Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents, one of seven sets of treatment guidelines issued by the federal HIV/AIDS Treatment Information Service (ATIS). ATIS is a DHHS project cosponsored by CDC, HCFA, HRSA, SAMHSA, the Indian Health Service, and NIH.
- NIAID actively participates in the Multilateral Initiative on Malaria - an alliance of organizations, including the World Health Organization, and individuals concerned with malaria research and control.
- NIAID jointly funds the Interdisciplinary Programs in Autoimmunity with the Juvenile Diabetes Foundation International. The programs focus on the immunologic and genetic mechanisms of the pathogenesis of several autoimmune diseases, including Type I diabetes.
- NIAID participated with other national research organizations in the Children's Vaccine Initiative, and undoubtedly will collaborate with the Global Alliance for Vaccines and Immunization when that new entity is launched.



#### **PLANNING AND PRIORITY SETTING**

NIAID planning and priority setting occurs in a larger context programmatic and resource allocation context. This context includes areas of emphasis determined by Congress, the Department, and NIH, a highly refined peer review process, the annual congressional appropriation, and other factors. Within that framework, NIAID plans programs of both intramural and extramural research.

Within the extramural program, NIAID supports studies initiated by individual investigators as well as those solicited by the Institute to address specific scientific opportunities, fill scientific gaps, and respond to insufficiently met public health needs. These opportunities, gaps, and needs are identified through research planning activities. NIAID may also steer the direction of unsolicited research through Institute-sponsored workshops and published research plans intended to stimulate research ideas in the scientific community. Ultimately, these activities affect the character of applications.

To ensure quality, all extramural research applications undergo an extensive, two-tiered review process. At the first tier, scientific review groups judge the merits of applications. At the second tier, the NIAID Council gives final approval to fund. Council funding considerations include policy considerations, such as the dearth of activity on urgent medical research questions.

The scientific merit of intramural research is assured through the laboratory review process. Every four years, the Board of Scientific Counselors, supplemented by *ad hoc* members, reviews each DIR laboratory. The reports and recommendations are presented to the Institute leadership. Intramural laboratory budgets are based on the NIAID allocation to DIR, the outcome of laboratory reviews by the Board of Scientific Counselors, relevance of the work to NIH and NIAID areas of emphasis, and other considerations, such as congressional mandates. Besides the basic budget for each laboratory, DIR allocates funds for special requests in order to advance studies in directions not accommodated or anticipated when the laboratory budgets were set.

### **THE ANNUAL NIAID PLANNING CYCLE**

NIAID implements a planning process to develop and select initiatives that solicit research applications to address special opportunities, gaps, and needs. The aim of the process is to maximize public benefit by: 1) paying close attention to current public health needs and anticipating changes in those needs; 2) capitalizing on scientific opportunity, especially on those with the prospect of reducing the burden of disease; 3) ensuring the capacity for future work by sustaining a broad array of basic research and nurturing scientific talent; 4) collaborating within and beyond NIH; and 5) using federal resources to leverage and complement the activities of other sectors. Being apprised of activities conducted by other government agencies, non-government organizations, as well as the pharmaceutical and biotechnology industry, is crucial to setting meaningful priorities.

NIAID's planning process was cited as a model by the Institute of Medicine (IOM) in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*. The structured process involves a progression of decision-making events informed by a continuous stream of reviews, evaluations, and consultations. The two pillars of this process are the Summer Policy Retreat (SPR), which is used to develop consensus on future scientific directions, and the Winter Program Review (WPR), which is used to discuss priority ranking of initiatives within each division's budget. Extramural research initiative concepts that are cleared by Council are implemented as Program Announcements (PAs), Requests for Applications (RFAs), and Requests for Proposals (RFPs). Intramural research initiatives are factored into the next year's allocation of funds for DIR.

Annual activities for development of research initiatives:

- Each fall, NIAID program officers review their scientific areas for the latest information on burden of illnesses and state of scientific progress. That activity lays the foundation for considering future plans.

- Scientific workshops, blue ribbon panels, and program reviews are held to evaluate progress in a field and determine future needs. These events typically involve the relevant scientific community and often the interested lay audience. The scientific questions and research plans articulated at these meetings influence both the nature of unsolicited applications and the special initiatives NIAID establishes.
- The NIAID Director and each division consult extensively with NIAID stakeholders; these consultations influence the issues and initiatives addressed during the structured planning process.
- Areas of emphasis selected by the Department, NIH, Congress, and others shape NIAID decisions to alter research course or initiate new activities.
- Participation in trans-NIH, PHS, DHHS, NSTC (National Science and Technology Council) and other coordinating committees affects the shape of NIAID research.

## **PUBLIC INPUT**

Public input is achieved in many ways. Representatives of voluntary health organizations and individuals based in health care are active on the NAAID Council. Also, NIAID's Executive Secretariat in the Office of Policy Analysis and its Office of Communications and Public Liaison establish and maintain strong links between the Institute and the public. These units respond to public inquiries, communicate NIAID news to the public, and funnel public concerns to appropriate NIAID divisions. Also, lay organizations actively participate in NIAID planning meetings. For example:

- The Directors of NIAID and the divisions frequently meet with lay organizations.
- On behalf of NIH, DAIT staffs the Coordinating Committee for Autoimmune Disease Research of which the *Ad Hoc* Coalition for Autoimmune Patient Groups is a member.
- PARA (patient advocates for Crohn's/*Mycobacterium paratuberculosis*) attended a workshop held, in part, to decide whether controlled antibiotic treatment trials are needed.
- Representatives of two patient advocacy groups are on the Advisory Panel for Clinical Studies in Chronic Lyme Disease and have made presentations to that group.
- DAIDS has been at the forefront in involving the community in all aspects of the research process.
  - ARAC. Community representatives sit on the AIDS Research Advisory Committee, which provides broad oversight and input, and advises the Director on programmatic plans and priorities.

- Each of the prevention, vaccine, therapeutic, and epidemiological research networks supported by DAIDS has a national and/or local Community Advisory Board (CAB). CABs are comprised of representatives from the volunteer research populations, such as: the parents of children with AIDS, individuals infected with HIV, and people at high risk for contracting HIV. The National CABs work with each network's leadership to develop a scientific agenda and set priorities. At the local level, CABs work with principal investigators to exchange information with the broader community and to assist with recruitment and retention of research subjects.

NIAID plans to expand upon and strengthen these interactions by exploring options, such as drawing public health officials into the planning of trials of behavioral and other prevention interventions.

### **DISEASES, DISCIPLINES, AND SPECIAL POPULATIONS**

To best serve public health, NIAID programs must balance *disease-centered* research - such as vaccine development for TB and other infectious diseases, and *discipline-centered* research - such as microbial genome sequencing. Often, NIAID initiatives will focus on a group of related diseases, like infectious diseases of the liver and gastrointestinal tract. This approach may be taken when important questions being addressed are common in both diseases. At times, this cluster approach is the best way to leverage limited resources. Sometimes, NIAID plans and programs must focus on a special population, such as when studying the mechanisms and pathogenesis of AIDS in children.

### **THE ROLE OF THE STRATEGIC PLAN**

This strategic plan builds on prior planning efforts and provides a framework for Institute activities over the next three to five years. It draws on insights from the annual planning cycle and cites published research plans. The plan also extends prior planning efforts by structuring a process through which the NIAID can articulate broad-based Institute-level priorities.

Although it establishes priorities, this plan is meant to be a flexible guide, not a rigid blueprint, for developing future programs, policies, and initiatives. Five years ago, there was little cause for concern about what today are some of our more pressing problems, such as defense against bioterrorism. Moreover, many of our most significant opportunities today could only have been imagined then, such as the use of DNA technology to understand microorganisms. Future shifts in need and opportunity are a certainty. Accordingly, NIAID will revisit this plan on an ongoing basis to accommodate change.

Research planning also is shaped by review of project proposals by NAAID Council and peer review groups. This process, which delegates considerable priority setting responsibility to scientific review groups, has proved to be the wisest means of selecting research projects most likely to advance science.

## **THE STRATEGIC PLANNING PROCESS**

The need to prioritize myriad opportunities is the primary motivation for this strategic plan. In addition, based on a recommendation in the IOM's 1998 report on NIH priority setting, the Office of the Director of NIH asked each IC to develop, with public input, a strategic plan with members of Congress and the public as its primary audiences.

Strategic plan development began in January 1999 with division staff outlining recommendations from the range of planning and consultative events NIAID has participated in and sponsored in recent years. The Institute developed a strategic planning framework organized around four cornerstones, or broad areas, that encompass the NIAID research portfolio: immune-mediated diseases, AIDS, emerging infectious diseases, and vaccines. In July, the Institute convened a [Strategic Planning Task Force](#) made up of scientist and non-scientist members and comprising a panel for each cornerstone. The panels deliberated the priority areas and suggested revisions to the draft plan. The next iteration of the plan was discussed during the September 1999 NAAID Council meeting. Following revisions prompted by the Council, the plan was posted on the World Wide Web for public comment during the month of November. This final draft, which reflects those comments, is being submitted to the Director, NIH, and will be discussed at the NAAID Council meeting in February 2000.

## **SCIENTIFIC OPPORTUNITY**

Years of investment in basic research have generated remarkable opportunities to understand immune-mediated and infectious diseases. As biomedical research moves into the post-genomic era, DNA technologies are profoundly altering the health research landscape, including the study of immunology and infectious diseases. The growing potential in these areas accounts for the numerous references to genomic-based studies in Opportunities and Plans within each of the four cornerstones. As scientists move from the study of single genes to groups of genes, from genomes to proteomes (all of the proteins in a cell), and from gene structure to gene function, they are:

- Revolutionizing approaches to understanding pathogenesis, microbial physiology, and epidemiology of infectious diseases.
- Radically advancing the understanding of immune activation and regulation.
- Uncovering the genetic basis of disease susceptibility.
- Accelerating the development of new diagnostic, treatment, and intervention strategies.

Many new opportunities derive from technologies developed just within the past five years. Advances in DNA sequencing methods, coupled with advances in computer programming, are dramatically accelerating the pace of genome sequencing. The ability to derive a pathogen's entire genome sequence is speeding up development of new diagnostics, treatments, and prevention strategies. Information from the human genome project, combined with technological advances such as polymerase chain reaction (PCR), is creating new approaches to determine the role of pathogens in chronic disease. DNA chips presage a revolution in diagnosis and treatment. Possible applications include: rapid diagnosis of infectious diseases; drug treatments customized to an individual's genetic

background; and routine screening for genetic diseases to identify susceptible individuals, so that preventive measures can be taken, or to relieve concern for unaffected individuals.

Recent advances in computer modeling, x-ray crystallography, combinatorial chemistry, and robotics are being harnessed for rational drug design and high-throughput drug screening. Advances will provide faster and cheaper drug discovery, more precise and effective pharmaceuticals, and drugs for diseases that have eluded previous treatment efforts.

Basic research has opened remarkable opportunities in other areas of immunology and infectious disease research. One of the most exciting, selectively blocking immune response, might be used to treat many immune-mediated diseases. In addition, these approaches may help achieve long-term, durable graft survival after transplantation. Basic research also is leading the way to new classes of drugs and vaccines. For example, the discovery that HIV binds to cellular co-receptors and that chemokines (cell signaling molecules) suppress this interaction reveals new targets for treating and preventing HIV infection.

Because research opportunities far surpass the resources available to explore them, it will be necessary to focus those resources on the most promising and urgent needs. This plan attempts to accomplish this by focusing on four broad areas: immune-mediated diseases, HIV/AIDS, emerging infectious diseases, and vaccine research.

## **PUBLIC HEALTH NEED**

### **THE IMPACT OF IMMUNOLOGIC DISEASES**

Immunologic diseases - asthma and allergy, primary immunodeficiencies, and autoimmune diseases - afflict millions of Americans and result in considerable illness, death, and medical costs. Also, transplant rejection, while not a malfunction of the immune system, nonetheless poses problems for treating many diseases for which the only treatment is to transplant tissue or an entire organ.

#### **Asthma and Allergies**

Asthma and allergies are major causes of illness and disability in the United States. One out of 5 Americans (more than 50 million) suffers one or both. Asthma is on the rise among U.S. children and disproportionately affects disadvantaged inner-city populations. Allergic diseases include allergic rhinitis, asthma, atopic dermatitis, urticaria, and anaphylaxis.

- In 1995, 14.8 million persons in the United States (5.7 of the population) were reported to have asthma and asthma was the first-listed diagnosis for 1.9 million emergency room visits. The disease cost an estimated \$14 billion in the United States during 1996.
- Chronic sinusitis is the most commonly reported chronic disease, affecting 14.1 percent of the population.
- Allergic rhinitis accounts for over 8 million outpatient visits per year.

- Anaphylaxis, the most severe form of allergic reaction, is a life-threatening reaction associated with cardiovascular collapse.
- Allergies to food, insect venom, and drugs can be severe, even fatal.

### **Autoimmune Diseases**

Autoimmune diseases, including insulin-dependent diabetes, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, are illnesses in which the immune system attacks the body's own tissues. While many autoimmune diseases are rare, collectively they afflict millions of people in the U.S. and a disproportionate number of women. The chronic nature of the diseases leads to high medical costs.

- *Insulin Dependent Diabetes Mellitus*. Also called type I diabetes, this disease is caused by immune destruction of the pancreatic cells responsible for the production of insulin. The resulting lack of insulin contributes to long-term complications affecting the kidneys, eyes, nerves, heart and feet. This disease afflicts an estimated 300,000 to 500,000 Americans, 123,000 of whom are under 20 years of age. The total costs for medical care, disability, work loss, and premature mortality are estimated between \$4.6 billion and \$9.2 billion annually.
- *Systemic Lupus Erythematosus (SLE)*. Approximately 240,000 Americans are diagnosed with or suspected of having SLE. This disease predominately affects women (greater than 90 percent of the cases) and is more common and severe among African American women. SLE damages multiple tissues and organs. Muscles, skin, joints, and kidneys, as well as the brain and nerves, may be affected.
- *Rheumatoid Arthritis (RA)*. An estimated 2.1 million Americans or about 1 percent of the population is afflicted with RA. It results in 25,000 hospitalizations per year, 2.1 million lost workdays annually, and 12 physician visits per patient, per year. RA usually begins as pain, swelling and tenderness in small joints of the hands and feet. Triggers of this inflammatory process, which are not completely understood, may destroy and deform the joints.
- *Multiple sclerosis (MS)*. A chronic, inflammatory disease of the central nervous system, MS is the second most likely cause of more than 30 percent limitation in physical and outdoor activities. The disease frequently results in permanent disability.
- *Graft Rejection*. Graft rejection results from a normal, healthy immune response aimed at transplanted tissue or an entire organ. For many people who suffer kidney failure, diabetes, leukemia, heart, and liver disease, the ultimate treatment must be tissue or organ transplantation. Yet, often transplants fail. Second only to organ shortage, graft rejection seriously impedes long-term transplantation success.

People with immunologic diseases, and those taking immunosuppressive drugs to enhance graft acceptance, carry not only the burden of the primary illness but, because of their compromised immune systems, they also are at high-risk for infections.



## THE IMPACT OF INFECTIOUS DISEASES

Infectious diseases are the second largest cause of death worldwide. In the United States they rank third. The economic impact of infectious diseases is also great, with an estimated annual cost in excess of \$120 billion. Prevalent and potential infectious disease threats include:

- *Acquired Immunodeficiency Syndrome (AIDS)*. In the United States, an estimated 271,000 people are living with AIDS. The rate of new HIV infections, approximately 40,000 per year, continues to be unacceptably high and minority populations are being infected disproportionately. Although AIDS deaths have fallen significantly during the past three years in developed countries, the need for next-generation therapies remains undiminished. A significant number of HIV-infected individuals is not responding adequately to current medications, cannot tolerate the toxicity of medications, or have difficulty complying with treatment regimens that involve extremely complicated and demanding dosing schedules. HIV persists in patients who appear to be successfully treated as they maintain extremely low bloodstream levels of the virus. Moreover, the emergence of HIV strains resistant to current drugs is a pressing challenge. In the developing world, the HIV/AIDS epidemic continues to accelerate. In 1998, HIV/AIDS was the fourth leading cause of death worldwide, resulting in an estimated 2.3 million deaths. Beyond the human tragedy of HIV/AIDS are economic costs, which pose a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Devising effective, low-cost tools for HIV prevention, such as a vaccine, is needed urgently to bring the HIV epidemic under control.
- *Tuberculosis (TB)*. TB is the eight leading cause of death worldwide. One-third of the world's population has latent TB, constituting a huge reservoir from which active TB can surface. Moreover, multi-drug resistant TB is an increasing problem.
- *Malaria*. In recent years, malaria has been undergoing resurgence with over 275 million new cases reported annually worldwide and an estimated death toll of 1.1 million. Increased parasitic resistance to prevailing drugs has reversed initial success in controlling this disease. The rise of malaria also is attributed to changing epidemiological and ecological patterns, increased resistance of mosquitoes to standard insecticides, and a lack of sustainability of existing control measures.
- *Influenza*. Pneumonia and influenza are the sixth leading cause of death in the U.S. killing 10,000 to 40,000 people in an average influenza season. Since 1918, at least three influenza pandemics have occurred. The worst, between 1918-1919, caused about 500,000 deaths in the U.S. and over 20,000,000 worldwide. In 1994, about 40 percent of the nation's population had an influenza-associated illness.
- *Hepatitis*. Hepatitis (liver inflammation) can be caused by a variety of viruses. The most common are hepatitis A, B, and C. Hepatitis A virus (HAV) causes acute liver inflammation and is generally transmitted from contaminated food or water. In 1998, over 28,000 cases of HAV were reported in the United States. Although HAV is the most prevalent form of hepatitis in the U.S., it leads to few deaths. However, this strain of virus can be deadly in developing countries. Hepatitis B virus (HBV) is an easily transmitted blood borne disease

that leads to chronic infections, especially in neonates infected at birth. Chronic HBV infection is a leading cause of liver cancer. In 1997, almost 9,000 cases of HVB were reported to the CDC. Worldwide, about approximately 1 million chronic HBV carriers die of liver cancer or cirrhosis during adulthood. Hepatitis C virus (HCV) also is blood borne. Almost 4 million people in the U.S. have been infected with HCV and 2.7 million are chronically infected. Liver damage occurs but may not cause symptoms for 20 or more years. About 85 percent of infected individuals eventually develop chronic liver disease, 20 percent develop cirrhosis, and a smaller percent liver cancer. About 9,000 people die annually from HCV and HCV accounts for over 1,000 liver transplants per year. Because the early stages of HCV are asymptomatic, many infected individuals unknowingly transmit the disease to others. Better diagnostics and blood safety procedures have driven incidence down from 180,000 in 1984 to 28,000 in 1994 to just over 4,800 in 1998. However, a good vaccine candidate still is needed.

- *Emerging Infections.* Numerous infectious agents are emerging from among the viruses, bacteria, protozoa, and fungi that make up the microbial world. Among viruses, HCV and hantavirus are the best-known, new infectious threats in the United States. Worldwide, however, dengue virus kills 5,000 children a year, fatal cases of monkeypox are reported from the Congo, and in 1997, evidence of a new paramyxovirus was isolated from pigs and can cause symptoms in humans. Tuberculosis, a bacterial killer, is classified as an emerging disease because multi-drug-resistant strains are evolving. Other emerging fatal bacterial infections include *Vibrio cholerae*, multi-drug resistant salmonella, and *Staphylococcus aureus*. The malaria parasite is also reappearing due to antimicrobial resistance. Other emerging parasitic diseases include *Cryptosporidium parvum*, *Cyclospora cayetanensis*, Chagas' disease, onchocerciasis, and neurocysticercosis. The incidence of new fungal diseases has increased dramatically and is an increasing problem, particularly for immunocompromised individuals. The fungus *Candida albicans* is a leading cause of hospital-acquired infection. Frequency of world travel makes the United States part of a global community. As a result, diseases that emerge in foreign countries represent significant health threats in the United States as well.
- *Bioterrorism.* Terrorist incidents involving biological agents are uniquely complicated because of the large number of potential agents, their long incubation periods and possible delayed onset of disease, as well as their potential for communicable spread. Unlike naturally occurring pathogens, agents used by bioterrorists may be genetically engineered to resist current therapies and evade vaccine-induced immunity.

## ACCOMPLISHMENTS

The outstanding contributions of NIAID-supported investigators extend from basic discoveries in microbiology and immunology to the development of diagnostics, drugs, and vaccines.

### IMMUNE-MEDIATED DISEASES

Decades of NIAID investment in research on processes of immune activation and regulation, and on the genetic bases of disease susceptibility, have yielded advances in the diagnosis, treatment, and

prevention of many debilitating diseases, including asthma and allergies, kidney transplantation, Wegener's granulomatosis and systemic vasculitis (both autoimmune diseases), some leukemias and lymphomas, and type 1 diabetes. These investments also have elevated our conceptual understanding of the immune system, thereby, positioning the field for significant clinical breakthroughs.

Basic research in immunology:

- Discovered mechanisms of antibody diversity.
- Defined humoral and cell-mediated immunity.
- Defined the role of the thymus in immunologic processes.
- Discovered immune response genes.
- Discovered the genetic bases of many primary immunodeficiency disorders.
- Discovered, at the molecular level, how the immune system mounts a response to a specific challenge, including: the description of the molecular structure of immunoglobulins; delineation of the role of major histocompatibility complex (MHC) proteins in the specificity of cell-mediated immune responses; delineation of the receptors on lymphocyte subsets; the discovery and characterization of cytokines; and the identification and characterization of T-cell receptors.
- Discovered methods of inducing tolerance in animal models.
- Discovered genes for many primary immunodeficiency diseases and developed highly effective therapies for their treatment.
- Utilized intravenous immunoglobulin for antibody replacement.
- Developed protocol for autologous bone marrow transplantation for treatment of some leukemias and lymphomas.
- Introduced interferon gamma for patients with chronic granulomatosis disease (a primary immunodeficiency disease).

Allergy and asthma research:

- Recognized the role of inflammation in allergic diseases and asthma.
- Discovered the role of viral infections in asthma.
- Discovered the significant role of indoor allergens as causes of severe asthma and developed a novel counselor-based intervention.

- Delineated the molecular mechanisms of the allergic response, including: discovery that IgE antibodies cause most allergic reactions; characterization of the IgE receptor; discovery of leukotrienes (chemical signals that mediate an allergic response); development of leukotriene-pathway inhibitors; and discovery of allergy and asthma genes.

Transplantation and immune tolerance research:

- Substantially improved renal allograft survival with new immunosuppressive therapies, which also allowed transplantation of a variety of other organs.
- Substantially improved genetic matching of organ donors and recipients through the identification and characterization of MHC genes.
- Demonstrated that ex-vivo co-stimulatory blockade prevents graft-vs.-host disease in bone marrow transplant recipients by tolerizing the graft to the recipient.
- Demonstrated the utility of intragraft gene expression as a potential early indicator of acute renal allograft rejection.

Autoimmunity research:

- Discovered the role of MHC in genetic susceptibility to autoimmune diseases.
- Identified the genetic loci of non-MHC autoimmunity.
- Discovered the interaction of the T-cell receptor and MHC with multiple non-homologous antigens.
- Demonstrated the role of molecular mimicry of self-antigens by pathogens.
- Defined the role of regulatory T-cell networks in controlling self-reactive cells.
- Developed immunomodulatory therapies, including cytokines and anti-cytokines, for treatment of many immunologic diseases including asthma and type 1 diabetes.
- Introduced the combination of glucocorticoids with cyclophosphamide for treating people with Wegener's granulomatosis and systemic vasculitis.

**ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)**

Considerable progress has been made in the area of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) since its emergence in 1981 as a deadly global infectious disease. In the United States and other parts of the industrialized world, the number of new AIDS cases and AIDS-related deaths has dropped dramatically. This has largely been the result of powerful new antiviral drug treatments that have prolonged and improved the quality of life for many HIV-infected people. NIAID-supported basic research has facilitated development of 16 licensed

antiretroviral drugs, and NIAID clinical trials have been pivotal in bringing many of these drugs to market. Significant discoveries include:

- Identified the HIV protease enzyme as a target for antiviral drugs, which led to the development of very potent protease inhibitors.
- Demonstrated the superior effectiveness of triple-drug treatments (combinations of protease inhibitors and reverse transcriptase inhibitors), often called "highly active antiretroviral therapy," or HAART, over one- or two-drug treatments.
- Discovered the role of HIV co-receptors and their interaction with chemokines as the basis for future anti-HIV strategies.
- Discovered the potential for cytokines in HIV/AIDS therapy.
- Discovered the means to prevent perinatal transmission of HIV, first by treating infected pregnant women and their infants with AZT, and more recently, by giving a single dose each, to mother and child, of the highly effective and relatively inexpensive drug nevirapine.

## **EMERGING INFECTIOUS DISEASES**

A multifaceted approach enables NIAID to meet the constantly evolving challenges posed by infectious diseases. Research endeavors to understand microbes, how they cause disease, and how they develop drug resistance and to use that knowledge to develop new diagnostic tools and interventions. Noteworthy accomplishments of NIAID-supported scientists include:

- Identified numerous human pathogens, including: *Borrelia burgdorferi* (Lyme disease), respiratory syncytial virus (bronchopneumonia in children), adenovirus, Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentine hemorrhagic fever), Norwalk virus, and others.
- Sequenced the genomes of numerous microbes, including: *Treponema pallidum* (syphilis), *Escherichia coli* strain K 12, *Chlamydia trachomatis*, *Plasmodium falciparum* chromosome 2 (malaria), and *Mycobacterium tuberculosis*.
- Conducted research that led to licensing of acyclovir as the therapy of choice for herpetic encephalitis.
- Developed diagnostics and treatments for Lyme disease.
- Supported a controlled clinical trial to evaluate intravenous ribavirin therapy for the treatment of hantavirus pulmonary syndrome (HPS).
- Responded rapidly to the outbreak of avian H5N1 influenza in Hong Kong by developing virus detection kits from antisera held in an NIAID reagent repository.

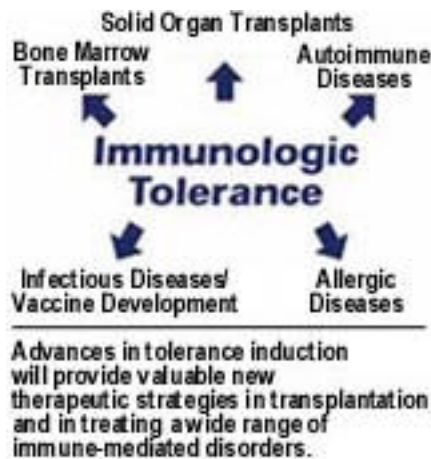
- Supported clinical trials of antifungal agents that greatly improved the therapies for systemic fungal infections, e.g.: developed the standard of care for cryptococcal meningitis; established the role of antifungal azoles in bronchopulmonary aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, candidiasis, and sporotrichosis; and established the value of newer formulations of amphotericin B in treatment of systemic mycoses.
- Identified the importance of blood group antigens in susceptibility to malaria, and identifying circumsporozoite and gametocyte antigens as vaccine candidates.
- Sequenced the TB genome, determined the mechanism of isoniazid (INH) resistance, and further elucidated the structure of the bacterial cell wall.
- Supported clinical trials that demonstrated the safety and efficacy of amantadine and rimantadine in the prevention and treatment of influenza A infections.
- Supported basic research to delineate the structure of the viral surface protein neuraminidase, which led to the development of a new class of antiviral drugs and the development and testing of live-attenuated influenza vaccines.

## **VACCINE DEVELOPMENT**

The value of vaccines in maintaining public health cannot be overstated. These powerful tools provide safe, cost-effective, and efficient means of preventing disease, illness, disability, and death from infectious diseases. Just four of the many vaccines developed recently by NIAID and its collaborators (hepatitis B, conjugate *Haemophilus influenzae* type B, acellular pertussis, and pneumococcal conjugate) have the potential to save millions of lives annually. As recently as 20 years ago, children worldwide frequently died of bacterial meningitis, while 1 in 200 U.S. children contracted *Haemophilus influenzae* type B (Hib), the primary cause of bacterial meningitis. A quarter of those who survived had brain damage or hearing loss. Today, thanks to NIAID-supported research, Hib is a rarity. Other vaccines developed with substantial support from NIAID include hepatitis A, adenovirus, typhoid, meningococcus, and influenza.

## THE CORNERSTONES OF NIAID'S STRATEGIC PLAN

### Immune-Mediated Diseases



The past two decades of intense and highly productive research on the immune system have resulted in a wealth of new information and extraordinary growth in conceptual understanding. These accomplishments now provide realistic opportunities for major advances in the diagnosis, treatment, and prevention of a broad range of human diseases. Advances in our understanding of immune regulation and the potential to uncover the genetic basis of disease susceptibility offer new means to confront many important diseases. Despite considerable gaps in knowledge, researchers are gaining an understanding of the complexities of immune activation and regulation within the physiological framework of the whole organism. As we enter the next century, these advances provide a solid foundation for translating basic research into clinical applications.

NIAID's strategic plan for immune-mediated diseases capitalizes on these extraordinary opportunities by focusing research efforts in several areas. Key topics include: 1) developing new tolerogenic and immunomodulatory approaches to treat autoimmune diseases, asthma and allergic diseases, and graft rejection in solid organ, tissue, and cell transplantation; 2) developing effective vaccines to prevent and treat immune-mediated diseases; 3) applying emerging technologies to advance fundamental understanding of immunologic principles and to develop better diagnostic and prognostic tools, improved patient monitoring techniques, surrogate markers of disease activity, and more effective therapies; and 4) continuing long-term support of fundamental discoveries of immune regulation that may ultimately be translated into practical applications for treating and preventing a broad range of diseases.

### BASIC IMMUNOLOGY

Continued investment in basic immunology research is a fundamental strategy to help ensure future progress in vaccine development, as well as in the diagnosis, prevention, and treatment of allergic and immunologic diseases. In addition to the preponderance of basic immunology research funded as investigator-initiated unsolicited grants, special programs have been used to promote advances in underserved areas. Programs in recent years include, Human Immunology Centers of Excellence, Vaccine Immunology Basic Research Centers, New Imaging Technologies for Autoimmune Disease, and Immunological Phenotyping of Mouse Mutants. The [Report of the NIAID Task Force on Immunology](#), published in 1998, summarizes expert opinions on a variety of research opportunities to pursue in the coming years.<sup>(1)</sup>

## Goals

- Standardize measurement of immune function at the cellular, biochemical, and molecular levels to facilitate understanding of disease pathophysiology.
- Maintain a pipeline of fundamental discoveries of immune regulation for translation into practical applications for vaccines and a broad range of immune-mediated diseases.
- Exploit immunologic principles to stimulate residual immune function in immunosuppressed individuals.
- Support underserved areas of research, such as: 1) immune regulation at specialized anatomical sites; 2) immune regulation at different stages of human development; and 3) the role of the innate immune system in regulating adaptive immunity.
- Integrate immune research with other research disciplines, such as cellular and molecular biology, tumor biology, neurology, genomics, proteomics, and bioinformatics.

## Opportunities and Plans

- *Biochemistry and Structural Biology of Immune Cells.* Biochemical definition of signal transduction pathways of immune cells is essential to advancing research in this area. The definition of these pathways with the aid of structural biology may help provide targets for drug development. Advances in the development of protein expression and purification systems, together with improvements in methods for structural determinations, provide significant opportunities to define immunologically relevant proteins at the atomic level. Such structural elucidations will allow the rational development of immunomodulatory drugs for novel preventive and therapeutic interventions in human disease.
- *Neonatal/Pediatric Immune System.* Even though most vaccines and disease treatments involve immune intervention at early developmental ages, little is known about immune capacity and immunoregulation in the neonatal and pediatric stages of human development. However, differences compared to adult immunity are known to exist, and increased research on those differences is expected to improve vaccination potential, as well as promote advances in treatments for food and airborne allergies, asthma, certain autoimmune diseases, pediatric organ and tissue transplantation, and immunodeficiency diseases.
- *Mucosal Immunology.* Immunity at the mucosal surfaces of the respiratory, intestinal, and reproductive tracts, as well as at the skin, can provide the first and most important defense against infectious pathogens. Because mucosal and systemic immune responses are often elicited and regulated independently, increased basic research is needed in this area. Mucosal immunizations are likely to be more relevant, simpler, and less expensive than systemic immunizations.



- *Innate Immune System.* Cells of the innate immune system, such as macrophages, neutrophils, and epithelial cells, express a variety of proteins that mediate antimicrobial responses by recognizing structures common to microbes but not found in mammalian cells. It is now clear that products of such innate, antigen-non-specific responses provide strong signals to help activate appropriate antigen-specific responses in T and B cells to promote long-lasting immune memory. Thus, the increased understanding of innate immune receptors and responses is important to advance progress in vaccine development.

## **IMMUNE TOLERANCE**

The successful induction of immune tolerance is a major goal for the treatment of many immune-mediated disorders, including autoimmune diseases such as rheumatoid arthritis, type 1 diabetes and multiple sclerosis; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. Advances in tolerance induction would provide valuable new therapeutic strategies that do not require life-long, globally immunosuppressive therapy, which has deleterious side effects. The ability to maintain a tolerant state will be equally important for preventing immune unresponsiveness to vaccines against tumors and infectious diseases.

### **Goals**

- Develop new tolerogenic approaches for the treatment of many immune-mediated diseases.
- Expand knowledge of the molecular basis for tolerance induction.

### **Opportunities and Plans**

NIAID has made immune tolerance a major priority and has developed a broad-based, long-range plan to accelerate research in this important area.<sup>(2)</sup> Major features of the plan include:

- Establish new and use existing clinical research infrastructures to accelerate multicenter studies.
- Integrate underlying mechanistic studies into non-human primate and clinical research.
- Facilitate partnerships with the pharmaceutical and biotechnology industries by creating infrastructures that will accelerate quality preclinical and clinical research.
- Invest in basic research to expand knowledge of the molecular basis for tolerance induction and maintenance and in innovative research to expand the universe of tolerogenic approaches.

Implementation of this research plan was initiated in FY 1999 with the establishment of several new research programs listed below:

- [The Immune Tolerance Network](#) co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Foundation International (JDFI), will conduct clinical trials of promising tolerogenic approaches, carry out integrated studies of underlying mechanisms, and develop surrogate/biomarkers of tolerance induction and maintenance. This new, multi-institutional research program is focused on four clinical areas: kidney transplantation, islet transplantation, autoimmune diseases, and asthma and allergic diseases.
- A Non-Human Primate Transplant Tolerance Cooperative Study Group will evaluate new tolerogenic reagents and molecules, as well as their underlying mechanisms.
- A cooperative program of Autoimmunity Centers of Excellence focuses on pilot clinical trials of promising tolerogenic and immunomodulatory approaches to treat multiple autoimmune diseases.
- In cooperation with NIDDK and the JDFI, NIAID is co-sponsoring clinical studies exploring new methods to induce tolerance to prevent graft rejection and recurrence of the autoimmune destruction of transplanted islets.

## TRANSPLANTATION

Transplantation is the therapy of choice for treating many diseases resulting in organ failure. Over the past two decades, significant improvements in surgical techniques, retrieval and preservation methods, and immunosuppressive therapy have greatly improved short-term clinical outcome. This progress has expanded the use of transplanted organs, tissues, and cells as potential new therapies for neurological disorders, malignancies, and autoimmune diseases. NIAID's long-term investment in molecular immunology has created extraordinary opportunities to accelerate the clinical application of tolerance induction therapies to achieve long-term, durable, graft survival while maintaining immune competence. NIAID is poised to capitalize on these promising opportunities as a means of overcoming major barriers to successful transplantation.

### Goal

- Improve both short- and long-term clinical outcomes by developing new therapeutic approaches to prevent graft rejection and by continuing the expansion of our knowledge of the mechanisms of immune rejection.

### Opportunities and Plans

#### *Immune Tolerance*

Successful tolerance induction and maintenance in the transplant setting will be fostered through solicited and investigator-initiated research programs, the Collaborative Network for Clinical Research in Immune Tolerance, and the Non-Human Primate Transplant Tolerance Cooperative Study Group.

#### *Immune-Mediated Graft Rejection*

While advances in the past five years have dramatically decreased rates of acute transplant rejection, the incidence of chronic rejection has not changed. Immune mechanisms responsible for chronic graft dysfunction and loss must be identified. To accomplish this, further research in humans is needed to:

- Define the non-immunologic factors leading to immune-mediated damage.
- Determine the role of subclinical rejection in pathogenesis of chronic rejection.

### **Transplantation Research Coordinating Committee**

The Transplantation Research Coordinating Committee is a congressionally mandated federal committee, which enhances communications among government agencies on solid organ, tissue, and cell transplantation issues. The committee, chaired by the NIAID, has representatives from appropriate NIH Institutes, as well as the Departments of the Army and Navy. In addition, representatives from the Office of the Secretary and DHHS agencies, such as the Division of Organ Transplantation of HRSA, AHCPR, and HCFA, regularly participate. The committee convenes three times a year to facilitate the exchange of information among relevant government offices about ongoing and planned transplantation activities.

- Determine the role of chronic infections (cytomegalovirus, hepatitis, respiratory syncytial virus, and Epstein Barr virus) in the pathogenesis of chronic rejection.
- Delineate the role of the above during identified phases of chronic rejection.
- Understand the immune response to injury, including immune recognition and activation, effector functions leading to inflammation, and regulatory functions leading to fibrosis.

### *Xenotransplantation*

The severe shortage of human organs suitable for transplantation has renewed interest in the potential use of organs obtained from other species. However, this approach has serious limitations, including: potential transmission of infectious organisms; inability to identify, quantify, and minimize the risks of infection to both recipients and the general public; absence of histocompatibility; and the possibility of delayed acute vascular xenograft rejection. Studies are needed to define the immune response to non-human antigens and assess cross-species infectivity, including:

- Identifying immunogenic xenoantigens and the immune recognition pathways for non-human antigens.
- Developing approaches that genetically manipulate donor animals or tissues to diminish immunogenicity or enhance resistance to host immune responses.
- Determining the probability of retroviral recombination leading to a new, pathogenic virus.<sup>(3)</sup>
- Assessing the risk of transmission of xenozoonosis (xeno-infectious disease), and developing new diagnostic methods to detect xenozoonoses before they become established infections.
- Evaluating *in vivo* safety and efficacy of antimicrobial therapeutics and the impact of viral mutants, alterations in pathogenicity, infectivity, and transmissibility of xeno-infectious organisms on these therapies.

### *Surrogate and Biomarkers of Graft Rejection and Immune Tolerance*

A major NIAID priority involves the development of assays and novel technologies to identify and validate surrogate markers of immune tolerance, disease stage, activity, and therapeutic response to predict long-term outcomes. Current NIAID-supported research includes analysis of cytokine expression using molecular techniques on biopsy and peripheral blood samples from transplant recipients in the Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation. These studies will be expanded to examine the non-invasive collection of samples, identify markers that can predict rejection prior to organ damage, monitor responses to therapy, and predict long-term outcomes. This will be accomplished through collaborations

among investigators within the kidney trial programs, the Immune Tolerance Network, and the Non-Human Primate Cooperative Study Group.

## **ASTHMA AND ALLERGIC DISEASES**

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. Significant increases in asthma prevalence, mortality and morbidity are of particular concern because of the disproportionate burden on disadvantaged, inner-city populations, especially on African-Americans and Hispanics. Recent scientific advances in understanding the genetic basis and immunologic mechanisms of asthma and allergic diseases provide new opportunities for prevention and treatment. These opportunities have been reviewed in department- and government-wide planning processes for asthma research, where NIAID efforts have been coordinated with those of other federal agencies.<sup>(4,5)</sup>

### **Goals**

- Develop more effective treatments for asthma and allergic diseases.
- Develop interventions to prevent disease onset.

### **Opportunities and Plans**

#### *Treatment of Asthma and Allergic Diseases*

Recent preclinical advances identifying several promising leads for immune-based therapies will be vigorously pursued. NIAID-supported research will focus more on studies of patients with asthma rather than animal models that mimic only some of the clinical features of asthma. These studies will capitalize on the accessibility of patients, clinical materials, and clinically validated tools to correlate airway functional responses with biological markers of immune activation and airway inflammation. Efforts to reduce asthma morbidity and mortality in inner-city populations will remain a primary aim of NIAID-supported research. An increased emphasis will be placed on developing and evaluating immune-based interventions, as opposed to behavioral and educational approaches.

Mechanism-based pharmacotherapies benefit particular subsets of asthmatic patients but not others, highlighting potential differences in disease pathogenesis. This, in turn, provides a foundation for mechanism-based clinical studies and functional genomic analyses.

While conventional immunotherapy has modest therapeutic benefit, concerns about its efficacy coupled with the difficulty of avoiding or eliminating indoor allergens have stimulated research on new approaches to selectively block (or tolerize) the immune response to allergen. Major research efforts will focus on:

- Developing tolerogenic and related approaches to block IgE production.
- Studying the regulation of T-cell subset development, as well as cytokine and chemokine expression in allergic and asthmatic inflammation.
- Defining signaling pathways in cells that participate in allergic and asthmatic inflammation.

*Primary Prevention of Asthma and Allergic Diseases*

Exposure to the cockroach, house dust mite, and other indoor allergens is recognized as a risk factor for increased asthma severity and the development of new-onset asthma. Preventing childhood asthma with appropriate interventions may be possible since immune modulation can be particularly effective in young children. Primary prevention of asthma may be clinically achievable and more cost-effective with immune-based interventions over therapies relying solely on allergen avoidance or elimination, or current medical therapies for established disease. Major research efforts will focus on:

- Conducting longitudinal studies of newborns and young children.
- Identifying genes and genetic polymorphisms as markers for disease development.
- Measuring immune responses to allergens that cause asthma and allergic diseases.
- Developing bioinformatics to correlate clinical data and genetic markers.
- Evaluating interactions between allergens and early life viral infections in development of asthma.
- Identifying and characterizing non-allergenic environmental factors that contribute to the onset of asthma.
- Identifying populations at high risk for developing asthma and allergic diseases, and developing tolerogenic or related approaches to prevent IgE production to allergens.

## AUTOIMMUNE DISEASES

Millions of individuals are affected by autoimmune diseases, but women are disproportionately affected. Alleviating or preventing the debilitating effects of autoimmune disease requires a broad strategy focusing on: identifying the mechanisms of disease induction, remission, relapse, and organ damage; delineating genetic susceptibility; defining the role of infectious and environmental factors in disease initiation or exacerbation; developing new therapeutic approaches; and eventually designing interventions, such as vaccines, to prevent disease onset.

### Goals

- Identify specific autoantigens in autoimmune diseases.
- Prevent the development of and effectively intervene in ongoing disease.

### Opportunities and Plans

#### *Vaccines for Autoimmune Diseases*

The Institute of Medicine report, *Vaccines for the 21st Century*,<sup>(6)</sup> and a recent NIAID meeting on vaccines for autoimmune diseases<sup>(7)</sup> highlighted the promise of vaccines for preventing and treating autoimmune diseases. Plans include:

- Continuing basic research, preclinical development, and clinical testing of tolerance induction.
- Developing antigen-specific and antigen-non-specific approaches.
- Developing therapeutic and preventive vaccines.
- Investigating the feasibility of oral tolerance and systemic tolerance induction pathways.
- Developing directed vaccination strategies to target genetically susceptible individuals or populations.

#### *Clinical Trials in Autoimmune Diseases*

NIAID is establishing mechanisms to translate basic research into clinical application. Approaches include immune modulation with antigen specific and non-antigen-specific agents, cytokines, costimulatory blockade, and anticytokines; and resetting the immune response using

### **Autoimmune Disease Coordinating Committee**

NIH established the Autoimmune Disease Coordinating Committee to foster collaboration and coordination of research in response to a congressional mandate. NIAID leads this committee, comprised of: interested NIH Institutes, Offices, and Centers; additional federal agencies, including the FDA, CDC, and the VA; private organizations supporting autoimmune research; and voluntary health agencies, such as the Juvenile Diabetes Foundation, the Crohn's and Colitis Foundation of America, National Multiple Sclerosis Society, and the American Autoimmune Related Diseases Association. The committee was instrumental in distributing \$30 million allocated by Congress for autoimmune disease research during FY 1999.

high dose chemotherapy, with and without stem cell reconstitution, and with and without damaged organ transplantation (islets, kidney, lung, joint, bone marrow). Gene transfer and gene therapy offers promising opportunities for tissue-specific modulation of immune response and target organ injury. Specific programs include:

- Immune Tolerance Network.
- Autoimmunity Centers of Excellence, which will combine basic research and clinical research in an environment of collaboration among multiple disease specialists, including neurologists, rheumatologists, endocrinologists, gastroenterologists, and clinical immunologists.
- Clinical trials to determine the efficacy of stem cell transplantation for autoimmune diseases.
- A program of hyperaccelerated awards, which supports mechanistic studies utilizing patients from funded clinical trials in immune-mediated diseases.
- Clinical trials of orphan autoimmune diseases.
- Clinical programs to develop markers of disease risk, activity, and therapeutic response.

#### *Autoimmunity Genes*

Genetic background appears to be a key element in the development of autoimmune diseases. Overlapping genetic susceptibility regions in different diseases are likely to represent genes or gene families that regulate autoimmunity, such as the major histocompatibility complex (MHC). Technology advances may allow researchers to identify certain genes regulating autoimmunity within the next five years. Research opportunities and plans include:

- Identifying autoimmune susceptibility and protective genes, including MHC and non-MHC.
- Identifying mechanisms of interaction of genetic regions in disease.
- Studying ethnic influences on genetic susceptibility and protection.
- Assessing environmental interactions with genetic background.
- Determining the mechanisms of gene action in susceptibility and protection.



### *Gender and Immunity*

It is not clear why autoimmune diseases are more common among women. Proposed explanations include microchimerism, which develops during pregnancy, sex hormones, and gender-based differences in the immune response. Research opportunities and plans include:

- Delineating the effect of sex hormones as well as the role of pregnancy and the menstrual cycle on the immune response and tolerance induction.
- Elucidating the role and mechanism of microchimerism in immune response and tolerance.
- Exploiting gender differences in animal models of autoimmune disease to understand mechanisms of hormonal effects on immune response.
- Delineating somatic and X-linked genetic influences on the immune response in autoimmune disease.

### *Environmental Factors and Infectious Agents in Autoimmune Disease*

Infectious agents have been associated with multiple autoimmune diseases. NIAID sponsored a meeting on the Role of Microbes in Autoimmune Diseases in February 1995.<sup>(8)</sup> Research plans and opportunities in this area are included in "Infectious Etiologies of Chronic 'Immune-Mediated' Diseases" below.

### *Immune Response and Neuroendocrine-Immune Interactions*

Recent advances in basic immunology have contributed to our understanding of self-tolerance, tolerance induction, and afferent and efferent pathways of the immune response. However, understanding of the mechanisms of these interactions is lacking and could aid development of new therapeutics. Research opportunities and plans include:

- Investigating the role of neural, neuroendocrine, and immune interactions in autoimmune diseases including lupus and multiple sclerosis.
- Identifying the role of environmental factors in the initiation and progression of autoimmune diseases.
- Understanding the role of cell death in induction and breaking of self-tolerance.

## **GENETICALLY DETERMINED IMMUNODEFICIENCY DISEASES**

Recurrent infections represent a significant health burden worldwide. While some infections occur in individuals with primary immunodeficiency diseases, susceptibility factors in the vast majority remain unknown. Enormous progress has been made in understanding the molecular

bases of a growing number of genetically determined immunodeficiency diseases owing to the gene-discovery tools provided by the Human Genome Project. Isolation of such genes is providing insights into basic mechanisms of immunology and guiding the development of novel treatment protocols.

Still, many disease mechanisms remain to be identified and characterized at the molecular level. In addition, understanding the basis of non-responsiveness to vaccines among apparently healthy individuals is an important goal for prevention of infectious diseases and could also contribute to understanding immune tolerance. Furthermore, determining the molecular basis of primary immunodeficiency disease is important for understanding the pathogenesis of autoimmune and malignant diseases, which occur with increased frequency among patients with primary immunodeficiencies.

### **Goals**

- Identify gene mutations that cause defects in the immune response leading to disease.
- Define the physiological roles of the proteins encoded by such genes.
- Develop effective therapies, including gene therapy, for immunodeficiency disorders.

### **Opportunities and Plans**

NIAID has supported productive investigator-initiated research on primary immunodeficiency diseases. In addition, the Institute, in collaboration with the Immune Deficiency Foundation, funds a registry for certain primary immunodeficiency diseases. To build upon these accomplishments, opportunities exist to:

- Expand the registry to include patients with all of the currently recognized genetically determined immunodeficiency diseases.
- Facilitate the molecular diagnosis of patients with immunodeficiencies.
- Support family/kindred studies to determine unidentified gene/chromosome locations for immunodeficiencies.
- Characterize poorly defined human primary immunodeficiency diseases.
- Define pathways of immune response in animal models and the relationship to human disease.
- Identify the functions of immunodeficiency-linked gene products in animals and humans.
- Develop gene transfer as a treatment for primary immunodeficiencies.

## **IMMUNOLOGIC BASIS OF EFFECTIVE HUMAN VACCINES**

Understanding human immunity is increasingly important for rational design and development of vaccines against major diseases, in which natural immune responses fail and there is little empirical guidance for vaccine development. How basic immunology can address the needs of vaccine research was the topic of a special Expert Panel meeting at NIH in 1998.<sup>(9)</sup> Participants highlighted areas of basic immunology research that have theoretical and practical importance for designing and developing effective vaccines. Support for increased collaborations between basic immunologists and clinical vaccine researchers is critically important.

### **Goal**

- Facilitate the rational design and development of vaccines by supporting research aimed at understanding fundamental principles of protective immunity in humans.

### **Opportunities and Plans**

#### *Protective Immunity Against Infectious Diseases*

Development of effective new vaccines and improvement of existing vaccines is hampered by an incomplete understanding of human protective immunity, especially the immunobiology of the target tissues and organs in specific disease states. NIAID plans to address this by continuing current funding mechanisms and adding support for collaborative research programs that discover, define, and analyze human protective immune responses to infection and vaccination (see [Request for Application \[RFA\] AI-99-008](#): Vaccine Immunology Basic Research Centers). Research programs will focus on:

- Defining immune system-pathogen interactions that shape immune responses.
- Identifying mechanisms of effector cell localization in target organs.
- Identifying critical effector functions in protective immunity and immunopathology.
- Understanding the development and persistence of immunologic memory.
- Exploring strategies to circumvent immune evasion by pathogens.

#### *Rational Design/Development of Vaccine Adjuvants and Immunostimulatory Strategies*

New strategies to increase vaccine effectiveness are needed to improve mucosal immunity, cellular or antibody-based immunity, and memory responses, and to reduce the need for multiple booster immunizations. Recent data on innate immune system function in initiating immune responses provides a systematic approach for developing effective immunostimulatory strategies. Collaborative studies between academic and industry investigators are needed to efficiently translate these insights into usable compounds for clinical studies. Programs will address:

- Characterization of cellular receptors that function in the immunostimulatory pathways triggered by microbes and microbial products.
- Development of candidate compounds that bind cellular or soluble receptors using large-scale screening, studies of structure-activity relationships, and immunologic assays.

#### *Therapeutic Vaccines for Chronic Infectious Diseases*

There are currently no vaccines developed or licensed to activate curative immune responses in the millions of individuals worldwide who have chronic viral, bacterial, parasitic, and fungal infections. Lack of theoretical and practical principles to guide therapeutic vaccine design and development has impeded progress in this area. Programs will be aimed at establishing basic information on immune responses that occur in chronic infection, as well as creating approaches to manipulate and enhance such responses in infected animal models and humans.

#### *Vaccines for Immune-Mediated Diseases*

NIAID will foster development of vaccines to prevent and treat immune-mediated diseases by selectively inactivating or modulating undesired immune responses. Vaccines are needed for autoimmune diseases, such as rheumatoid arthritis, insulin-dependent diabetes mellitus, and multiple sclerosis; transplantation, including acute and chronic rejection of organs and tissues; asthma; and allergies. Research will focus on:

- Identifying specific antigens to anergize, delete, or modulate deleterious lymphocytes.
- Controlling inflammatory responses by cytokines, cytokine-inducing substances and costimulatory molecule blockade aimed at inflammatory cells.
- Activating regulatory T cells to reduce inflammation in target tissues.

### **INFECTIOUS ETIOLOGIES OF CHRONIC IMMUNE-MEDIATED DISEASES**

Infectious agents are major contributing or causative factors in the development of many chronic diseases. In fact, infectious agents cause 16 to 20 percent of all cancers, and mounting evidence indicates that they may be the underlying causes of chronic diseases, such as coronary artery disease, diabetes, multiple sclerosis, autism, and chronic lung diseases. Recent technological advances, such as consensus polymerase chain reaction (PCR), combined with emerging human genome sequence information, provide promising new opportunities to identify non-human genetic material in diseased tissue. The identification of infectious agents as causative factors in chronic disease will revolutionize clinical diagnosis and treatment of these debilitating conditions and provide unique opportunities to prevent many diseases through new vaccine development. In June 1999, the NIAID-National Cancer Institute workshop, Infectious Etiologies of Chronic Diseases, focused on steps needed to define the role of infectious agents in the initiation and progression of chronic diseases.<sup>(10)</sup>

## **Goals**

- Develop cross-disciplinary programs with the capacity to identify infectious agents involved in the initiation and maintenance of human chronic diseases.
- Define mechanisms by which infectious agents and/or the immune response cause disease pathogenesis.

## **Opportunities and Plans**

### *Epidemiology*

Large-scale longitudinal studies of patients are necessary to determine infectious agent-chronic disease associations. Two critical parts of these epidemiology studies are the acquisition and proper handling of patient specimens and detailed clinical databases. These studies will be used to identify and establish priorities among candidate disease-pathogen pairs.

### *Diseases for Initial Study*

While many chronic diseases may prove to be triggered to some extent by an infectious agent, recent scientific findings point to several chronic diseases and pathological processes to serve as promising candidates of study. These include certain malignancies, autoimmune diseases such as type 1 diabetes, multiple sclerosis, and Crohn's disease; granulomatous diseases, such as Wegener's Disease and sarcoidosis; enteropathic arthritides; asthma; and atherosclerosis.

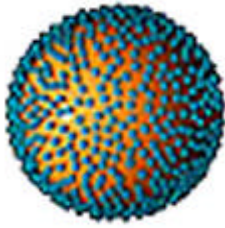
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- Summary of NIAID Extramural Transplantation Research Program Review, September 22-23, 1998 (Letter from Drs. Auchincloss and Bluestone)
- NIAID Workshop on Clinical Trials for Immune System Mediated Diseases, 1996
- [Summary of Workshop on Prospects for Gene Therapy of Inherited Phagocyte Disorders](#), 1998
- [Summary of the Workshop on Systemic Vasculitis: Future Research Directions](#), 1997
- [Primary Immunodeficiency Diseases](#), 1997

## **Acquired Immunodeficiency Syndrome (AIDS)**



*The AIDS Virus*

Since HIV was first identified in 1983, enormous progress has been made in understanding how the virus attacks the immune system to cause disease and in how to intervene therapeutically. NIAID-supported scientists have led much of this progress. New techniques have enabled researchers to detect HIV in blood and tissue, and new therapies have achieved excellent results in suppressing the virus and delaying disease progression and death. NIAID-funded researchers have also made great strides in reducing mother-to-infant transmission of HIV. In the area of prevention research, 27 different vaccines have been evaluated, and efforts are under way to increase the number of new vaccine and microbicide candidates that can be tested.

Despite this progress, complex scientific obstacles and questions remain before AIDS can be effectively controlled. Research is needed to identify new strategies and tools to accelerate drug and vaccine discovery, to better understand immune reconstitution, and to determine the most promising drug candidates. Viral drug resistance remains a major obstacle to effective, long-term therapy, and new therapeutic regimens are necessary to minimize viral replication and burden in the body. Research on new therapies must also assess the metabolic complications and long-term effects of antiretroviral treatment. For vaccine development to move forward, questions about the significance of latently infected resting T cells, HIV and human leukocyte antigen (HLA) diversity, correlates of immune protection, and the applicability of different animal models must be answered. Finally, for HIV prevention efforts to have a global impact, effective, inexpensive, and easily administered regimens need to be developed, especially with regard to mother-infant transmission. NIAID is well positioned to tackle these scientific challenges through its vaccine, prevention, therapeutic, and basic research programs. Based on the current state of scientific knowledge, research plans in each of these areas complement each other to achieve NIAID's overall AIDS research goals to prevent the continued spread of HIV infection, and reduce the sickness and death associated with it. The specific objectives and strategies for accomplishing these goals are highlighted below. They are consistent with and draw upon the NIH-wide FY2000 Plan for HIV-Related Research and the draft FY2001 version of that plan.

### **EPIDEMIOLOGY**

Epidemiologic research provides information that advances our understanding of the biology and clinical course of HIV infection. NIAID's epidemiology studies focus on cohorts of individuals who are either at high risk for HIV infection or are already infected. These individuals are seen regularly and followed over long periods. Comprehensive data and biological sample collections provide a complete picture of HIV infection and disease, and serve as a unique resource for investigations of immunologic, virologic, genetic, and other factors that may modulate the various stages of HIV disease.

## **Goal**

- Understand the changing pattern of HIV infection throughout the world, and the impact of therapeutic, vaccine, and other prevention-based interventions on survival and clinical outcome.

## **Opportunities and Plans**

- Identify and characterize the risk factors and mechanisms of HIV transmission in different parts of the world to understand why and how people continue to be infected with HIV.
- Determine the incidence and prevalence of adverse health outcomes, including cardiovascular diseases, diabetes, metabolic complications, opportunistic infections (OIs), and co-morbidity with other infections.
- Determine the role of host genetics in susceptibility to HIV infection, disease progression, and immune response.
- Determine the prevalence of drug-resistant HIV and its relationship to disease.
- Determine the epidemiology of treated patients, and the effects of therapeutic and preventive interventions on infection, morbidity, and mortality in domestic and international populations.
- Develop and evaluate improved methods for epidemiologic studies, including culturally relevant recruitment and retention approaches; improved laboratory, sampling, and statistical methods; and informatics.
- Conduct studies on the effects of highly active antiretroviral therapy (HAART) on virologic and immunologic markers of disease progression and long-term effects in diverse populations, including post-exposure and high-risk cohorts.
- Conduct epidemiologic studies to ascertain the prevalence of HIV-1 clades, HIV-2, tuberculosis, and hepatitis C.
- Conduct studies to determine the short-term, intermediate, and long-term effects of cost-effective antiretroviral therapy during pregnancy and after delivery, on the mother and newborn in domestic and international populations.
- Develop and maintain domestic and international infrastructures for epidemiology studies.

### **New and Continuing Programs**

- Address the pathogenesis of disease progression among HIV-infected women and their children – *Women and Infants Transmission Study (WITS)*.
- Follow the long-term history of HIV-infected and at-risk individuals – *Multicenter AIDS Cohort Study (MACS)*.
- Investigate the natural history of HIV infection in women in the United States – *Women's Interagency HIV Study (WIHS)*.
- Study host immunogenetic characterization, including HLA types and T-cell epitopes – *HLA Typing and Epitope Mapping to Guide HIV Vaccine Design Program*.

### **PATHOGENESIS**

HIV pathogenesis research increases our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. NIAID supports HIV pathogenesis research investigating: mechanisms of viral entry and infection; the structure, function, and mechanism of action of viral genes and proteins; and studies of how the immune system responds to the virus. Knowledge gained from these studies enhances the ability of researchers to create new agents and vaccines to combat HIV infection. These efforts have yielded significant scientific information about HIV, including the identification of new structures for viral components of HIV, co-receptors, and the existence of multiple, persistent HIV reservoirs in human tissues. Despite these advances, questions still remain about the molecular interactions that regulate HIV expression and replication. More information is also needed about how the virus evades the immune system in order to identify additional targets for therapeutic interventions and vaccines.

### **Goal**

- Understand how HIV causes disease.

### **Opportunities and Plans**

- Define the cells or tissues that serve as initial target sites of infection, the role of viral genotypes/phenotypes, and the HIV dose required for establishment of HIV infection.
- Define the mechanisms of HIV persistence in cell and tissue reservoirs, mechanisms of latent virus reactivation, and the impact of low-level viral replication on transmissibility.
- Define direct and indirect mechanisms of T-cell depletion, and enhance and expand innovative studies on human immunology to guide immune reconstitution and vaccine development efforts.



- Define the etiology and pathophysiology of treatment-related metabolic abnormalities in adults and children.
- Define the mechanisms underlying HIV-associated neurological disease and neurobehavioral dysfunction in adults and children.
- Define the pathogenic mechanisms of HIV-related opportunistic infections (OIs) in adults and children.
- Identify new viral and cellular targets for therapeutics, microbicides, and vaccine development based upon new insights into HIV biology and HIV-host interactions.

### **New and Continuing Programs**

- Support investigator-initiated, hypothesis-driven HIV/AIDS pathogenesis research.
- Provide infrastructure and promote basic, clinical, behavioral, and translational AIDS research at institutions that receive significant AIDS funding from multiple NIH Institutes or Centers – *Centers for AIDS Research (CFAR)*.
- Examine molecular and cellular biology, virology, and immunology in animal models, human cohorts, or patient samples – *Mechanisms of AIDS Pathogenesis: Collaborative Teams (MAPS)*.
- Study HIV-1 pathogenesis utilizing data and biological specimens from and coordinated with the Multicenter AIDS Cohort (MACS) Pathogenesis Research Laboratories.
- Study mechanisms of mother-to-infant HIV-1 transmission and pathogenesis of HIV-1 infection in infants and children – *Mechanisms And Pathogenesis Of Pediatric HIV-1 Infection*.
- Formulate and test specific hypotheses for HIV/AIDS pathogenesis in women – *HIV Pathogenesis in Women's Interagency HIV Study*.
- Provide state-of-the-art biological and chemical materials to support HIV research – *NIH AIDS Research and Reference Reagent Program, including the NIAID Tetramer Facility*.
- Support repositories for specimens from HIV epidemiology, therapeutic, vaccine, and other prevention research studies.
- Support pathogenesis research on acute and early HIV-1 infection – *Acute Infection and Early Disease Research Program*.

## **TREATMENT**

NIAID-sponsored therapeutics research has had a dramatic impact on the clinical management of HIV infection over the past decade. NIAID clinical trials networks have defined international guidelines for: (1) the treatment of primary HIV infection and associated opportunistic infections; (2) prophylactic regimens for secondary infections; (3) biological markers, such as CD4+ counts and HIV-1 viral load for predicting drug effectiveness and disease progression; and (4) the use of antiretroviral drugs for preventing mother-to-infant transmission. More recent studies have shown that highly active antiretroviral therapy (HAART) – regimens of at least three antiretroviral drugs, (i.e., reverse transcriptase inhibitors and usually at least one protease inhibitor) – is capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV morbidity and mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance and/or non-adherence to complicated and often toxic regimens. Moreover, damage to the immune system is not fully reversed. Thus, there is an ongoing, urgent need for new therapeutic agents to control HIV replication and boost, rebuild, and/or replace immunity lost in HIV infection.

## **Goal**

- Extend the gains in survival and quality of life achieved by current therapy by minimizing the adverse effects of long-term treatment and, ultimately, to cure HIV infection.

## **Opportunities and Plans**

- Optimize antiretroviral therapy for untreated and pretreated HIV-infected patients to minimize development of drug resistance, enhance tolerability, contain costs, and improve long-term patient outcomes.
- Determine the regional and global patterns of resistance to antiretroviral therapies and their impact on long-term antiretroviral treatment efficacy, and develop effective therapies for individuals with drug-resistant HIV.
- Develop and evaluate new agents and treatment strategies to destroy or inhibit the expression of HIV in tissue reservoirs and latently infected cells.
- Develop and evaluate therapeutic approaches to enhance, restore, and/or maintain the immune systems of HIV-infected individuals. Determine whether HIV-directed immune responses can be augmented in infected individuals, and if so, whether it benefits the patient.

- Define the structure and function of potential molecular targets and agents for the prevention and treatment of HIV-associated opportunistic infections (OIs), including drug-resistant tuberculosis, *Mycobacterium avium* complex (MAC), cytomegalovirus, *Pneumocystis carinii*, and hepatitis C virus.
- Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system disorders in HIV-infected individuals.
- Develop and evaluate improved therapies for the treatment and prevention of serious HIV-associated complications, including metabolic and body composition disorders, wasting syndrome, growth failure, and other systemic manifestations.
- Determine the safety of antiviral agents in pregnant women, including transplacental passage of agents and fetal safety.
- Determine in newborns the pharmacokinetics, metabolism, tissue absorption, and elimination of antiviral drugs.
- Develop improved mechanisms for assessment of long-term outcomes in clinical trial settings.
- Develop long-term drug trials targeted at acute and early HIV infection.
- Reduce the complexity of treatment regimens and develop strategies to improve treatment adherence.
- Define biological markers associated with effectiveness and durability of response to therapies to permit individualization of therapies and simplification of clinical trial design in an era of diminishing clinical endpoints.
- Develop strategies for promoting effective health care utilization among persons with HIV infection. Promote modifications in the health care delivery system to better serve the testing and treatment needs of disenfranchised and culturally diverse populations.
- Develop international collaborations to assist in answering critical therapeutic questions by including populations of HIV-infected patients outside the United States and in developing countries.

### **New and Continuing Programs**

- Evaluate innovative therapeutic strategies and interventions for adults with HIV/AIDS and its complications, including opportunistic infections (OIs) and neurological disorders associated with HIV/AIDS – *Adult AIDS Clinical Trials Group (AACTG)*.

- Conduct clinical trials in adults to evaluate the long-term benefits and unintended consequences of various treatment strategies – *Terry Bein Community Programs for Clinical Research on AIDS (CPCRA)*.
- Evaluate therapeutic strategies targeted at acute and early HIV infection – *Acute Infection and Early Disease Research Program*
- Evaluate the efficacy of drugs and drug combinations for treating HIV infection and HIV-associated illnesses in infants, children, adolescents, and pregnant women – *Pediatric AIDS Clinical Trials Group (PACTG)*.
- Support preclinical discovery and development of new and improved therapeutics – *Novel HIV Therapies: Integrated Preclinical/Clinical Program* and *HIV Therapeutics: Targeting Research Gaps*.
- Support chemical and biological databases, pharmacology, toxicology, analytical chemistry, and drug manufacturing for the development of new HIV therapeutics – *Chemistry and Pharmaceutical Resources for Therapeutics Development Program*.
- Provide tissue-based small animal models for HIV drug discovery, and in vitro virologic and immunologic evaluations for anti-HIV drugs and microbicides – *In Vitro and Animal Model Testing Resources for Therapeutics Development Program*.
- Support development of new therapies to treat AIDS- and cancer-associated opportunistic infections (OIs) – *National Cooperative Drug Discovery Research on Opportunistic Infections*.
- Support development of new strategies for the prevention and treatment of complications of HIV and HIV therapy – *Therapeutics Research on AIDS-Associated Opportunistic Infections and Collaborations for Advanced Strategies in Opportunistic Infections and HIV-Associated Complications*.
- Support acquisition, screening, and animal model testing of potential therapeutics, screening for activity in microbiological systems and animal models of tuberculosis, and assistance with development and licensing of candidate drugs without corporate sponsorship – *NIAID Tuberculosis Drug Development*.

## **HIV VACCINES**

The discovery and development of a vaccine that protects against HIV infection is one of the highest priorities of the NIH AIDS research program. A great challenge of vaccine research is the need for contributions from a variety of disparate fields of science (e.g., basic science, empiric animal testing, human trials) to develop an efficacious vaccine. NIAID's comprehensive vaccine program has led to a number of significant scientific advances. NIAID-supported researchers have made strides in elucidating the structure of HIV, understanding the role of the immune system in controlling HIV, improving vaccine antigenicity, and developing new and better animal models for testing candidate vaccines. To accelerate identification of effective vaccine candidates, future studies will need to address the significance of latently infected cells, immune responses induced by current vaccine candidates, and the impact of HIV and HLA diversity. In addition, because the majority of new HIV infections are occurring in the developing world, strong international collaborations will need to be formed and ethical issues addressed in order to conduct efficacy studies in those countries. The coordination of this complex program of AIDS vaccine research is an important function of NIAID.

### **Goal**

- Identify and develop safe, effective vaccines to protect people from HIV infection and disease.

### **Opportunities and Plans**

- Identify mechanisms of protective immunity and host defense to HIV in adults, newborns, and infants, and develop assays to measure these immune responses.
- Build upon recent knowledge regarding the establishment of HIV infection to develop and test a broad range of new vaccine strategies, alone or in combination, to induce selective immune responses (e.g., humoral, cellular, mucosal, and systemic) against primary non-syncytium inducing virus and CCR5-using HIV isolates from all genetic clades.
- Design viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiological, and clinical research.

### **HIV/AIDS Vaccine Coordinating Activities**

NIAID is the principal organization in all substantial federal HIV/AIDS vaccine coordinating activities. These committees are led by senior NIAID officials. Dr. Anthony S. Fauci, NIAID Director, heads the AIDS Vaccine Subcommittee of the Committee on Health and Safety and Food Research and Development, of the White House's National Science and Technology Council. He also leads the Public Health Service Subcommittee on AIDS Vaccine Development. Dr. Peggy Johnston, NIAID's Assistant Director for HIV/AIDS Vaccines, chairs the NIH Office of AIDS Research Coordinating Committee on HIV Vaccines.

- Develop and utilize simian-human chimeric viruses (SHIV) with different degrees of virulence to more closely reflect disease progression in humans and the genetic variation observed worldwide.
- Improve animal models and the availability of non-human primates for systematic, comparative efficacy testing of vaccine concepts; improve understanding of the protection mechanisms that might be translated to HIV vaccine studies in humans; and evaluate candidate vaccine strategies in animal models.
- Identify domestic and foreign populations in which to define and assess seroincidence and genetic subtypes, as well as determine and optimize feasibility of vaccine studies in appropriate cohorts.
- Conduct domestic and international vaccine trials in populations at risk for HIV transmission via different routes.
- Advance the most promising candidate vaccines to Phase 1 and Phase 2 clinical trials and, if safe and immunogenic, then to larger, Phase 3 trials to determine efficacy.
- Evaluate how or whether individuals at high risk for HIV infection alter their behavior as a result of participating in a vaccine trial.
- Identify and develop broadly effective, polyvalent anti-HIV functional antibody combinations or other products for prophylaxis of HIV transmission alone or in combination with vaccination and/or short-term antiretroviral prophylaxis.
- Develop safe and effective vaccine strategies and passive immune interventions for preventing or controlling HIV infection in newborns and infants worldwide.
- Open NIAID programs to international researchers to ensure that the best approaches worldwide are pursued vigorously by the best researchers possible.
- Foster early and continued collaboration with industry on research and development of candidate vaccines, and test a broad array of vaccine concepts and combinations of different approaches for potential HIV vaccine products, including vaccines for particular populations.
- Coordinate NIAID research efforts with the NIH Vaccine Research Center (VRC).
- Develop strategies, infrastructure, and collaborations with governments and communities to ensure adequate performance of vaccine trials, while balancing the prevention needs of at-risk populations.

## New and Continuing Programs

- Support investigator-initiated HIV vaccine research.
- Carry out a comprehensive HIV vaccine research agenda focused on the clinical evaluation of promising HIV vaccine candidates – *HIV Vaccine Trials Network (HVTN)*.
- Encourage the entrance of novel and innovative vaccine discovery and development concepts into the research pipeline – *Innovation Grant Program: Approaches in HIV Vaccine Research*.
- Support investigator-initiated HIV vaccine research where investigators have collected significant preliminary data – *HIV Vaccine Research and Design (HIVRAD) Program*.
- Support development and production of HIV vaccines for clinical trials – *HIV Vaccine Production Contract*.
- Provide procurement and/or production of reagents essential to AIDS vaccine development and evaluation, as well as quality assurance testing of these reagents – *Vaccine Reagent Resource*.
- Support laboratory-to-clinic development, evaluation, and refinement of vaccine concepts – *Integrated Preclinical/Clinical AIDS Vaccine Development*.
- Support consortia of scientists to advance vaccine concepts toward a vaccine product within a five-year period – *HIV Vaccine Design and Development Teams*.
- Compile, analyze, and disseminate HIV genetic sequence and associated data worldwide – *HIV Database and Analysis Unit*.
- Provide non-human primates for immunization with candidate SIV or HIV vaccines – *Simian Vaccine Evaluation Units*.
- Support the development of methods for evaluating immune responses to vaccines – *Laboratory Methods to Assess Responses To HIV Vaccine Candidates*.
- Support research on the human mucosal immune system relevant to the design of HIV vaccines and other preventions – *Mucosal Immunity in Pathogenesis/Prevention of Human Disease*.

## **NON-VACCINE PREVENTION STRATEGIES**

The AIDS epidemic continues to take its toll worldwide, despite major advances in understanding the pathogenesis and treatment of HIV infection. Control of the epidemic will probably require a combination of prevention strategies to protect against HIV infection, even in the presence of an efficacious vaccine. Such strategies include methods to interrupt mother-to-infant transmission of HIV; biomedical approaches, such as topical microbicides and the treatment of sexually transmitted diseases (STDs); and behavioral interventions. Given the global dimensions of the epidemic and urgent need to find methods to halt transmission worldwide, NIAID supports a range of prevention research activities in both domestic and international settings.

### **Goal**

- Identify safe, efficacious, cost-effective non-vaccine interventions to prevent the transmission of HIV.

### **Opportunities and Plans**

- Develop biomedical strategies to inhibit transmission of HIV through exposure to HIV-containing blood, tissues, and other fluids. Candidate strategies include topical microbicides, HIV-specific virucides, and systemic antiretroviral agents.
- Develop biomedical strategies to interrupt vertical transmission of HIV from mother to child in developed and developing countries, and in breastfeeding and non-breastfeeding populations using interventions that are widely affordable, accessible, and practical in those populations.
- Identify host, gender, extrinsic and viral factors and cofactors, including other STDs, that affect HIV transmission, and assess interventions to slow viral transmission in at-risk domestic and international populations.
- Develop and evaluate effective social and behavioral interventions at the society, community, organization, social network, dyadic, and individual levels to prevent HIV transmission and acquisition by reducing risk behaviors and increasing protective behaviors. Interventions should address the risks in their social and cultural contexts both domestically and internationally.
- Identify the determinants, processes, cultural and contextual issues influencing infection-related risk and protective behaviors, and the consequences and impact of HIV disease, including treatment for and management of HIV infection.
- Develop and evaluate strategies to prevent or minimize the negative physical, cognitive, and social consequences of HIV, including stigmatization of persons with or at risk for HIV infection.



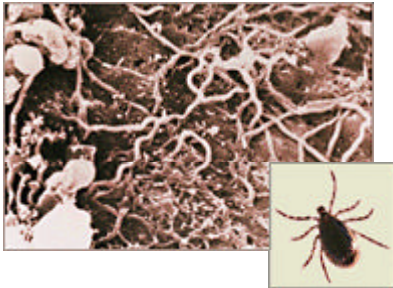
### **New and Continuing Programs**

- Conduct domestic and international research on promising biomedical and behavioral strategies for the prevention of HIV transmission – *HIV Prevention Trials Network (HPTN)*.
- Evaluate interventions designed to reduce mother-to-infant transmission of HIV-1 – *Pediatric AIDS Clinical Trials Group (PACTG)*.
- Conduct multidisciplinary biomedical and behavioral research in disease mechanisms, vaccines, diagnosis, and treatment – *Sexually Transmitted Disease Cooperative Research Centers*.
- Evaluate candidate topical microbicides in preclinical studies and clinical trials, and develop behavioral interventions to ensure acceptance and use of topical microbicides – *Topical Microbicide Program Projects*.
- Support the preclinical development of topical microbicides – *In Vitro, Animal Model, Chemical and Pharmaceutical Resources Program*.

### **RESEARCH PROGRAM PUBLICATIONS**

- [The National Institutes of Health FY2000 Plan for HIV-Related Research](#)

## Emerging Infectious Diseases and Global Health



*Lyme spirochete/tick*

Infectious diseases are among the leading causes of death worldwide, and they are expected to remain a major public health threat.<sup>(1)</sup> Despite remarkable advances in medical research and treatments during the 20<sup>th</sup> century, menacing infectious diseases persist for three reasons.

- **Emergence of New Infectious Diseases.** Twenty years of improving diagnostic and detection methods have revealed several previously unknown human pathogens, such as *Borrelia burgdorferi*, *Helicobacter pylori*, *Cyclospora cayatenensi*, and hepatitis E and C viruses. Evidence suggests that pathogens may play a role in some diseases previously thought to be chronic and noncommunicable. *H. pylori* has been implicated in gastric ulcers and cancer, for example, and *Chlamydiae pneumoniae* in cardiovascular disease. Population sprawl and behaviors that bring people into closer and more frequent contact with pathogens are also contributing to the rise in infectious diseases. In some cases, this involves increased exposure to animals or insects that carry disease. Examples include the potential role of primates in transmission of HIV and Ebola virus, of rodents in transmission of hantavirus, and of tick vectors as well as rodents and deer in transmission of Lyme disease.
- NIH Lyme Disease  
Coordinating Committee**

Lyme disease affects several organ systems of the body. Since 1992, the NIH Lyme Disease Coordinating Committee has met annually to coordinate research efforts among NIH Institutes. The committee reviews results of current studies and research advances.
- **Re-Emergence of Old Infectious Diseases.** Natural genetic variations, genetic recombination, and environmental selection lead to new strains of known pathogens - influenza virus and *Vibrio cholerae* 0139, for example - against which humans have little or no defense. Microbial development of antibiotic resistance resulting from increased and sometimes imprudent use of antimicrobial drugs and pesticides has allowed tuberculosis, malaria, nosocomial, and foodborne infections to make a comeback. Bioterrorist release of deadly pathogens into the civilian populations theoretically could also re-establish infectious diseases.

- *Persistence of Intractable Infectious Diseases.* Around the world, diarrhea, respiratory, and parasitic diseases are major killers of young children; sexually transmitted diseases take their toll on mothers and infants.<sup>(2)</sup> Increasing interdependence among nations through travel, commerce, the globalization of food supply, population migrations, urbanization, and environmental issues make world health a concern for every country. Recently, the United States has seen outbreaks of food and waterborne infections, as well as mosquito-transmitted viral fevers, illnesses once considered health risks only in developing countries.

The NIAID is interested not only in the human diseases caused by infectious agents, but also in the agents themselves. The public health importance of a microbe is a function of the prevalence, mortality, morbidity, and economic impact of human infection caused by the microbe. The relative public health importance of many infectious agents has changed throughout recorded history as a consequence of improvements in sanitation, development of vaccines, discovery of antimicrobial drugs, and advances in medical therapy. Apart from their public health importance many microbes are also worthy of investigation because they serve as model organisms for the study of fundamental biological processes. Given that the resources required to investigate all microbes capable of causing human disease are far greater than those available to NIAID, the Institute must prioritize microbes for study by considering their public health importance, their potential to reveal fundamental physiologic and pathogenic processes, and the research opportunities being pursued in other sectors, e.g., industry.

NIAID has been actively involved in planning and implementing research on emerging diseases and global health. The Institute supports various initiatives of the Institute of Medicine (IOM), such as a 1992 study entitled, *Emerging Infections: Microbial Threats to Health in the United States* and the ongoing Forum on Emerging Infections. In addition, the Institute participated in a 1995 government-wide planning process resulting in recommendations listed within *Infectious Disease - A Global Health Threat*, by the National Science and Technology Council (NSTC), Committee on International Science Engineering and Technology (CISET), Working Group on Emerging and Re-Emerging Infectious Diseases. In 1996, NIAID provided its own plan for addressing these issues by publishing the *Research Agenda for Emerging Diseases*. The Institute is pursuing this agenda through a number of programs. Some programs broadly address issues relevant to disease emergence and international health while others focus on specific disease problems. Government-wide planning is continuing for many important emerging diseases. Recent examples of joint planning by federal agencies include the Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance, and the Research Agenda for the Rapid Development of Diagnostic Tools, Treatments, and Vaccines for Diseases Caused by Bioengineered Biological Warfare Agents. In

#### **Emerging Diseases Research Goals**

- Strengthen basic and applied research on the multiple host, pathogen, and environmental factors that influence disease emergence.
- Support the development of diagnostics, vaccines, and therapies necessary to detect and control infectious diseases.
- Maintain the national and international scientific expertise required to respond to future health threats.

[From the 1996 NIAID  
Research Agenda for  
Emerging Diseases.](#)

addition, NIAID and other NIH components participate in international planning and coordination efforts, such as the Multilateral Initiative on Malaria and the *Plasmodium falciparum* Genome Sequencing Consortium.

Many logistical and scientific challenges stand in the way of better prevention, treatment, and control strategies for emerging diseases and those infectious diseases that primarily impact the developing world. Leadership from the public sector is needed to provide incentives for increasing involvement by the pharmaceutical industry. Support for research to identify product leads, as well as help with clinical evaluation, can reduce costs and risks for industry and thus facilitate the process of getting new public health tools on the market.<sup>(3)</sup> A major NIAID goal is to establish and fortify links among the biomedical industry, government agencies, international organizations, and private foundations to assist in the public health application of research findings.

## **MICROBIOLOGY AND VECTOR BIOLOGY**

A plan to prepare for future infectious disease challenges must emphasize fundamental research to improve prediction and prevention. This will begin with expanded studies in microbiology and infectious disease ecology. Research in specialized fields such as molecular biology, genetics, cell biology, population and evolutionary biology, mathematical modeling, computer science, and remote sensing technology is essential to this effort.

### **Goal**

- Enhance our ability to predict and prevent conditions that lead to human disease by understanding the complex dynamic between and among pathogens, potential host carriers, and the environment.

### **Opportunities and Plans**

NIAID broadly supports research in microbiology and vector biology through grants to extramural researchers, as well as intramural research programs aimed at cross-disciplinary development and applications of new technology. NIAID also encourages these projects through special solicitations. During FY 1999, NIAID and the National Institute of General Medical Sciences (NIGMS) requested research proposals on the evolution of infectious diseases (see [Request for Application GM-99-005: Evolution of Infectious Diseases](#)). This initiative supports population and evolutionary studies related to causes and sources of infectious diseases, interactions between hosts and pathogens, consequences of intervention strategies, variation in pathogen virulence and host susceptibility to infections, and the natural history of pathogenic organisms. More recently, NIAID has joined with several other Government agencies to support research on the relationship between man-made environmental changes and transmission of infectious diseases (see [Request for Application TW-00-002: Ecology of Infectious Diseases](#)). Future NIAID-supported studies will focus on whole-genome approaches to pathogen research, including large-scale sequencing, bio-informatics, and functional genomics. Such investigations

will provide tools critical to the study of microbial evolution, adaptation, and pathogenicity. Future research areas include:

- Studying the adaptive mechanisms that allow microbes to become more pathogenic. Facilitating research on: molecular evolution; the genetic basis of host range or tissue specificity; the genetic basis of virulence; the influence of microbial interactions, microbial competition, and host-pathogen interactions; and the acquisition of new genetic elements (lateral gene transfer).
- Elucidating methods by which pathogens moderate their virulence and discourage superinfection, thereby ensuring self-preservation.
- Conducting zoonotic research that compares pathogenic effects of a microorganism in different hosts to obtain unique insights into disease mechanisms and examining pathogen/host interaction in terms of differences in both microbial function and host immune response.
- Supporting multidisciplinary research that defines the impact of environmental changes on emergence and/or increased transmission of infectious diseases.
- Supporting vector biology and ecology research (as well as research training) to identify and define factors that influence the opportunity and ability of invertebrates to serve as vectors for infectious diseases.
- Applying technological advances, such as mathematical modeling and satellite-based remote sensing, to improve understanding of transmission dynamics in order to predict future disease outbreaks.

## **DIAGNOSIS AND DETECTION**

Rapid, sensitive methods for pathogen identification, disease diagnosis, determination of the drug sensitivity of microbes, and determination of the pesticide sensitivity of arthropod-vectors, would significantly increase the quality of patient care and simplify infectious disease surveillance and control programs. This is especially true for emerging diseases where surveillance and control decreases the likelihood of an epidemic. Such tools are critical for effective public health programs and also important to national preparedness against biological warfare.

Between 1990 and 2020, deaths from noncommunicable diseases are projected to increase by 77 percent. Ischemic heart disease and cerebrovascular disease are expected to rank first and fourth, respectively.<sup>(4)</sup> This projection comes at a time when new research suggests that cardiovascular disease and many other "noncommunicable" diseases are caused or exacerbated by infectious agents. The potential health burden of these diseases warrants more extensive analysis of the contributions of infectious agents to chronic diseases.<sup>(5)</sup> Such studies will also require new diagnostic tools and expanded epidemiological studies. The link between *H. pylori* and gastric ulcers provides an example of how identifying infectious causes of noncommunicable diseases can open new avenues in prevention and treatment.

### **Goal**

- Strengthen our ability to diagnose human infectious diseases and detect pathogens in the environment.

### **Opportunities and Plans**

NIAID is developing a comprehensive program of pathogen genome sequencing and post-genomics research (see NIAID Policies for Large-Scale Genome Sequencing Projects, <http://www.niaid.nih.gov/dmid/genomes/policies.htm>). Institute-supported programs seek to identify specific and shared microbial genes as well as to create specific gene expression assays.

Findings from the Human Genome Project, the Trans-NIH Mouse Initiative, and various sequencing projects of model organism genomes complement this effort and are expected to yield insights into the genetic basis of human susceptibility to infection and disease.

The Institute is participating in the ongoing Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance. NIAID's influenza program is developing diagnostic reagents against subtypes of avian influenza virus with high pandemic potential. Additional efforts include the Small Business Innovation Research (SBIR) grant program, which provides the opportunity to support development of diagnostic assays for infectious diseases within the biotechnology industry. Development of assays and therapeutic monitoring systems for clinical and vaccine trials are areas of emphasis within the program announcement for [Small Business Innovation Research Advanced Technology, SBIR-AT-NIAID](#). Future NIAID programs will seek to develop methods to rapidly detect hospital-acquired infections and drug resistance of those organisms. In addition, the Institute will foster research on diagnostic tools for detecting bioterrorism agents and the infectious etiology of chronic diseases. Future research opportunities include:

#### **NIAID-NCI Working Group on Human Papillomavirus (HPV) Research**

A recent understanding of how infectious diseases can contribute to some cancers has prompted interactions between NIAID and NCI. NIAID heads the NIAID-NCI Working Group on Human Papillomavirus (HPV) Research, an informal association of intramural and extramural scientists, which meets on an *ad hoc* basis. Primary objectives include the expansion of genomic databases containing data on sexually transmitted pathogens, the evaluation of therapeutic and prophylactic vaccines for HPV infection, and the evaluation of HPV detection methods.

- Supporting large-scale microbial sequencing projects that develop genetic probes for surveillance and screening. These probes will identify specific microbes as well as detect genetic polymorphisms associated with differences in drug sensitivity, transmission, and virulence. Additional probes will identify shared sequences among related microbes to facilitate rapid classification of emerging pathogens.
- Extending efforts to develop or improve indirect assays for pathogen identification. This includes serologic response to the microbe or virulence factors and newer methods such as T-cell profiling.
- Developing quantitative assays to evaluate the efficacy of prevention and treatment protocols within clinical trials.
- Working with industry to advance the development of high-throughput diagnostic assays that are sensitive, specific, noninvasive, and easily used in the field, such as those based on analysis of urine or saliva.
- Developing genomic methods to detect the expression of pathogen genes and proteins in host tissue, and correlate gene and protein products with specific disease manifestations.
- Supporting clinical and epidemiologic studies, such as large-scale longitudinal studies, which can provide access to isolates of "real world" pathogens and help identify the molecular basis of virulence and pathogenesis.
- Expanding efforts to understand the role of infectious agents in causing poorly understood chronic diseases, such as cancer, cardiovascular, digestive and neurological diseases. Examining the potential role of "nonpathogenic" organisms acquired during childhood. Linking survey studies to basic research efforts to prove causality and establish mechanisms of pathogenesis, including the potential role of human genetics.

## **TREATMENT**

Research to develop new chemo- and immunotherapies begins with a basic understanding of microbial physiology and the host-pathogen relationship. The goal is to identify targets of vulnerability during the complex processes of colonization, replication, and eventual transmission to new hosts. Translating research discoveries into new or improved therapies requires specialized resources and infrastructure. Recent advances in structural biology, computer modeling, crystallography, combinatorial chemistry in drug design, and robotic technology for high-throughput screening must be harnessed to identify and produce candidate compounds for therapeutic use. Partnerships with the biotechnology and pharmaceutical industries are ideal for accomplishing this successfully. Specialized resources must be made available for preclinical and clinical testing of new therapeutics, including scale-up and pharmacokinetics. Finally, the design of therapies against unknown pathogens, whether naturally



emerging or the result of bioengineering, poses a special challenge and emphasizes the need for developing better broad-spectrum antimicrobial agents.

## Goal

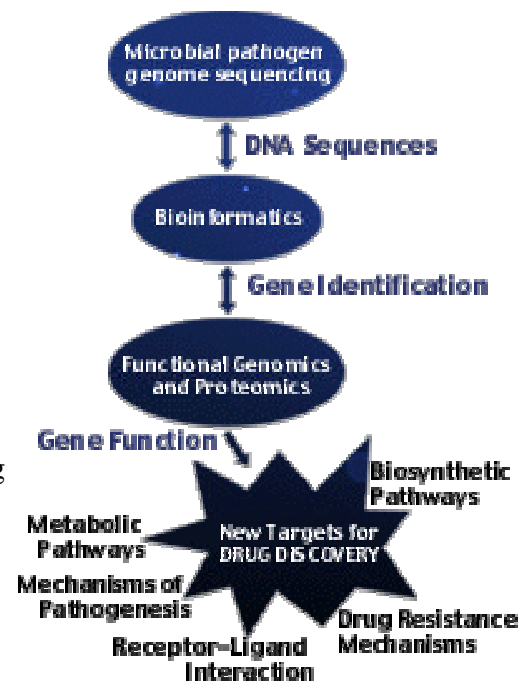
- Develop new and improved methods for treating illness, controlling outbreaks, and preventing epidemics.

## Opportunities and Plans

Most of the fundamental research efforts in this area will continue to be conducted under individual investigator-initiated research grants. Research may be encouraged by program announcements such as that on [Molecular and Structural Approaches to Antiviral Strategy](#). NIAID's concerted initiative on pathogen genomics and post-genomics research is expected to make important contributions in identifying critical metabolic pathways, receptor-ligand interactions, and other microbial functions that could serve as targets for potential antimicrobial drugs. This information can benefit the design of high-throughput screens used to identify inhibitors to serve as "leads" in drug development.

Specialized resources for drug development and testing are best maintained through solicited grant and contract programs. NIAID will continue to support facilities to screen antiviral compounds in vitro and in appropriate animal models. Support will also continue for clinical testing programs, such as the Mycoses Study Group, the Cooperative Antiviral Study Group, and the Vaccine and Treatment Evaluation Units. Developing the required interactions with industry, however, remains a challenge. NIAID has created incentive for the biotechnology industry to target research on emerging and other orphan diseases through its program announcement for Small [Business Innovation Research Advanced Technology, SBIR-AT-NIAID](#), which emphasizes the development of targeted therapies and drug delivery systems. Major opportunities include:

- Supporting the identification of molecular mechanisms and biochemical pathways that are critical to the function of viral, bacterial, fungal, and parasitic pathogens. More specifically, these include host cell receptors that mediate the initiation or maintenance of infection; factors that control the synthesis and function of toxins and/or virulence factors; host-defense mechanisms; and metabolic processes that play a decisive role in the ability of pathogens to grow and persist in the body.





- Encouraging training in microbial physiology, comparative medicine, genomics, and bioinformatics, as well as skills for translational medicine (e.g., clinical epidemiology, clinical trials, biostatistics). Examining new strategies to boost training in gap areas.
- Expanding the application of advances in computer modeling and synthetic chemistry to develop inhibitors of critical microbial functions, which may serve as lead compounds for drug development.
- Supporting comparative genetics of bacterial, viral, fungal, or parasitic organisms to identify common molecular pathways that can serve as potential drug targets against currently known pathogens and related pathogens in the future.
- Supporting the design of immune-based agents such as monoclonal antibodies, immunomodulators, and immunoglobulins.
- Developing culture systems and small animal models to facilitate development of drugs for emerging/re-emerging infectious diseases.
- Expanding access to facilities for pilot lot production of candidate therapeutics.
- Supporting trials that examine the utility of antimicrobial treatment in chronic diseases where research suggests an infectious etiology.
- Working with the biotechnology and pharmaceutical industries to encourage pursuit of preclinical and clinical research to further develop drugs to prevent and treat infectious diseases.

## **DRUG AND INSECTICIDE RESISTANCE**

Diseases that were once controlled but are now re-emerging because of resistance to antimicrobial drugs present additional research challenges. Development of resistance is fueled by increased and/or inappropriate drug use and amplified by person-to-person or common-source transmission in crowded settings such as hospitals. Tuberculosis, gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat due to the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired (nosocomial) infections, and many are concerned that some infections may soon become untreatable. The need for long-term treatment of many chronic viral infections, such as hepatitis B virus, also leads to the development of resistant strains. Agricultural practices may also influence disease re-emergence. In affluent countries, antibiotics are extensively used to treat domestic animals and livestock, adding selective pressure on microbes. Similarly, the widespread usage of pesticides on agricultural crops leads to the selection of resistant insect vectors that pass on disease.

## **Goal**

- Develop new strategies to control diseases that are re-emerging due to drug or insecticide resistance.

## **Opportunities and Plans**

The Institute is providing leadership for research planning by way of the new Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance. The NIAID Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) provides an infrastructure to coordinate research on the following: 1) full microbiological characterization of strains of *S. aureus* with intermediate susceptibility and resistance to the antibiotic vancomycin; 2) epidemiology of pathogenic organisms to determine the extent of and risk factors for their development and spread within hospital settings and the environment; and 3) clinical testing of interventions for preventing, controlling, diagnosing, and treating infections in humans due to these organisms. Future studies on hospital-acquired infections will emphasize clinical strategies that decrease frequency of infection and reduce emergence of antimicrobial resistance. Investigator-initiated research grants support studies to understand the basis of drug resistance in tuberculosis, malaria, and other re-emerging diseases, as well as the nature of insecticide resistance in mosquitoes and other invertebrates. Genomics studies should help identify the molecular basis of drug resistance, as well as factors influencing the spread of resistant organisms, and may reveal new control options. Some possibilities include developing improved assays for drug susceptibility under the recently renewed Tuberculosis Research Unit program and molecular epidemiology studies of tuberculosis supported by the International Collaborations in Infectious Diseases Research. Through its contribution to the Multilateral Initiative on Malaria, NIAID is also helping to identify molecular markers for drug resistance in malaria and to monitor the spread of drug and insecticide resistance in Africa. Additional opportunities include:

- Expanding genomics research to identify and characterize the molecular basis of drug resistance to develop better surveillance and diagnostic tools, and to aid in developing novel treatments and preventive strategies.
- Expanding epidemiological and modeling studies to assess the effectiveness of available control measures in areas where drug resistance currently occurs or is likely to appear.
- Supporting studies of alternative administration regimens for existing drugs, including dose manipulation and combination therapy.
- Identifying new usage indications for existing therapies, such as the control of trachoma-induced blindness by azithromycin.
- Exploring alternative and supplemental therapies such as micronutrients and naturally occurring antimicrobial peptides.

- Supporting research in entomology to identify alternative environmentally friendly methods to replace commonly used insecticides for vector control.

## **GLOBAL HEALTH**

Improving our global ability to combat infectious diseases that are resistant to current control strategies presents many unique research challenges. Basic research is needed to understand how pathogens evade normal host defenses and to identify potentially vulnerable points in that process, which may present target sites for new control methods. In addition, epidemiological and field-based research on the natural history of disease, as well as access to facilities and resources for developing and evaluating new control strategies within endemic countries, is critical to resolving global health issues. Long-term, sustainable support for collaborative international research and training programs provides an important opportunity to improve global health and prepare for future infectious disease threats.

### **Goal**

- Identify better control strategies for intractable infectious diseases that continue to challenge global health.

### **Opportunities and Plans**

The Institute has developed comprehensive research plans for a number of infectious diseases of global importance, including HIV/AIDS (as described under the AIDS section of this plan), tuberculosis, malaria, influenza, sexually transmitted diseases, hepatitis, and food/waterborne infections. Many of these focus on vaccine development (as described under the Vaccine section). Genomics, microbial physiology, epidemiology and natural history, and development of improved diagnostics and therapies are also important areas of emphasis. Diseases of international health importance also present additional scientific and logistical challenges, such as access to endemic sites and populations. The Institute will continue to support field-based research through investigator-initiated grants, disease-specific initiatives, as well as special programs such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers. Major opportunities include:

- Research on the mechanisms of infection persistence, latency, and reactivation.
- Research on mechanisms allowing pathogens to evade or circumvent host defenses, such as molecular mimicry or antigenic variation.
- Research aimed at intervening in disease transmission by an invertebrate vector, such as insects or ticks.
- Research on the mechanisms of pathogenesis, including the role of pathogen and host response during infection, to identify novel strategies to ameliorate disease symptoms despite ongoing infection.

- Genetic epidemiology studies to understand the role of host genes or single nucleotide polymorphisms in susceptibility or resistance to infection. These may enable identification of at-risk populations and facilitate treatment and control efforts in resource-poor countries.
- Field- and population-based studies of natural disease cycles to determine points of vulnerability that may offer opportunities for disease control.
- Research to identify environmental and behavioral risk factors for infectious diseases with poorly understood modes of transmission.
- Improved access to field sites and populations where infectious diseases are endemic to validate new control measures.
- Strengthened research, surveillance, and response capabilities of other countries through collaborative programs and training.

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## **Vaccines**

The discovery of a vaccine to prevent smallpox in 1796 led to one of the greatest achievements of medical science - eradication of a disease. Widespread use of vaccines to prevent infectious diseases is one of the greatest public health achievements of this century. NIAID's long-term focus on vaccine discovery and development has significantly contributed to that achievement. The Institute takes a leadership role from the development of fundamental information on host-pathogen interactions to the conduct of clinical trials of new vaccine candidates. Basic science and applied research, fueled by NIAID investments, are creating unprecedented opportunities to expand vaccine discovery and development within the next five years.<sup>(1,2)</sup> Advances from NIAID-funded vaccine research include:

- Broader knowledge of the molecular aspects of virulence.
- Expanded knowledge of fundamental human immunology, including mucosal immunology.
- Development and evaluation of new immunomodulators.
- Development of novel vector/delivery systems, such as genetically engineered vaccines.
- Increase in the number of human and microbial sequence platforms, including expression microarrays, bioinformatics, and other associated tools.
- Enhanced ability to recognize the full spectrum of the immune response to a vaccine.

Based on scientific opportunities and public health needs, NIAID's Strategic Plan for vaccines is focused in four areas: 1) vaccine discovery, design, and development; 2) development of vaccines against pathogens associated with emerging and potentially re-emerging global health problems; 3) overcoming obstacles to development of vaccines against pathogens of high public health importance that have eluded preventive intervention; and 4) vaccine development in newly identified areas of need.

### **VACCINE DISCOVERY, DESIGN, AND DEVELOPMENT**

Understanding human immunity, analyzing the molecular dynamics of binding complexes during host/pathogen interactions, and utilizing the pathogen and host gene expression profiles will become increasingly important for the discovery, design, and development of future vaccines. Investigators should be encouraged to direct this knowledge base toward discovery and development of safe and effective vaccines as public health tools to prevent infectious diseases in relevant populations and climates. Translation from the discovery phase to the design and development of vaccines is difficult and will require early recognition of practical needs, such as single dose, temperature-stable formulations, delivered by novel routes (skin, nose).

## **Goals**

- Facilitate the discovery, design, and development of vaccines through expanded knowledge of the molecular and immunologic interplay between host and pathogen.
- Foster collaborative interactions among various disciplines to accelerate progress in vaccine discovery, design, and development.

## **Opportunities and Plans**

Increased knowledge from basic research will advance development of new approaches to discovery, design, and development of protective antigens, as well as the rational improvement of existing vaccines. Therefore, commitments to sustain and build on the foundation of basic and clinical research, strengthen infrastructure, and promote collaborations, underlie each targeted area. Such commitments include:

- Studying microbial pathogenesis and mechanisms of immune evasion.
- Studying and understanding microbial/host interactions that shape the immune response.
- Exploring the immune response to infection, including optimization of response with adjuvants, cell targeting, and enhanced recognition of microbial antigens or epitopes.
- Understanding the role of the innate immune system in modifying specific immune responses.
- Exploring the unique challenges associated with vaccine development for immunocompromised individuals.
- Dissecting critical effector functions in protective immunity.
- Understanding the development and persistence of immunologic memory.
- Exploring strategies to circumvent immune evasion by microbes.
- Studying the interplay between host and pathogen using microbial and human genomics.
- Using post-genomic technologies, such as microarray analysis, proteomics, and bioinformatics, to further probe host and pathogen biology by 1) understanding the molecular basis for rare adverse responses to vaccines; 2) accelerating the identification of immunologic correlates of protection; and 3) exploring the immunologic and biological basis of non-response.
- Enhancing understanding of the protective mechanisms of currently effective vaccines.

- Utilizing expertise, experience, and supportive infrastructure within relevant federal agencies, global institutions, and the private sector to achieve the goal of developing and universally implementing safe, effective, and relevant vaccines for improvement of national and global health.
- Partnering with the pharmaceutical and biotechnology industries on vaccine development strategies of mutual interest and high relevance to public health.
- Targeting impeded or orphan vaccines of low priority to U.S. industry and those particularly important to developing countries.
- Developing novel cross-disciplinary training programs to fully exploit opportunities in microbial genomics, proteomics, informatics, engineering, and biology to be applied to vaccine discovery, design, and development.

#### **PATHOGENS ASSOCIATED WITH EMERGING AND RE-EMERGING GLOBAL HEALTH PROBLEMS**

Improving our ability to predict which microbes will emerge as new or more deadly pathogens requires a broad and stable research program on all human pathogens. Emerging pathogens may be rapidly self-limiting, such as Ebola virus, or chronic with relentless persistence or worsening, such as hepatitis C virus.

Pathogen emergence and re-emergence are influenced by a variety of factors. Changes in lifestyle, such as urbanization, have altered ecological boundaries and led to the emergence of diseases such as Lyme disease and dengue. Changes in social behavior have led to an explosive re-emergence of some sexually transmitted diseases. The increased use of day-care centers has been accompanied by an increase in congenital cytomegalovirus infections. Climatic alterations affect the emergence of vector-borne infections, such as hantavirus and Rift Valley fever.

Common pathogens previously killed by antimicrobial drugs, such as *Streptococcus pneumoniae* and *Salmonella typhi*, may begin to re-emerge as highly resistant and potentially dangerous organisms. Newly resistant pathogens (multi-drug resistant TB, for example) may manifest and be particularly severe in immunocompromised individuals, representing an important area for vaccine development. Previously unknown pathogens will begin to be identified as isolation and detection procedures become more sensitive and immunosuppressive procedures more prevalent. Increasingly, the ease of global interactions has exposed highly susceptible populations to diseases not previously encountered. Despite the breadth of potential needs, the basic research requirements associated with the development of vaccines against emerging infections is similar.

#### **Goal**

- Support broad and stable research programs that will rapidly expand vaccine development for emerging and re-emerging pathogens associated with global health problems.



## **Opportunities and Plans**

NIAID will continue to emphasize the importance of basic research in vaccine development. In addition, it is essential to continue support of a versatile clinical infrastructure to allow flexible and rapid development and testing of candidate vaccines against newly emerging and re-emerging pathogens. These include the ability to rapidly:

- Establish a scientific base to permit the understanding of emerging infections. The following are critical to anticipate the burden of disease, define optimal methods of control, and assess readiness for vaccine development:
  - Utilize or develop epidemiologic data to define anticipated disease burden, risk populations, and likelihood of public health importance.
  - Develop animal models for newly identified emerging pathogens.
  - Identify antigens or epitopes that stimulate protective immune response to newly emerging pathogens.
  - Identify host-pathogen interactions that limit the host's ability to develop a protective immune response or permit evasion of the immune response.
  - Identify conserved antigens or epitopes in ecologically evolving or re-emerging pathogens, as well as those with multiple serotypes/genotypes that may limit effectiveness.
  - Characterize the impact of genetic reassortment, mutation, and evolution of re-emerging strains on the protective immune response elicited by parent strains.
- Take advantage of strategic alliances with industry to ensure that a vaccine will confer optimal protection and maximum safety through a program that will:
  - Process development of a candidate vaccine.
  - Produce pilot lots of candidate vaccines.
  - Evaluate candidate vaccines in Phase 1 and 2 trials.
  - Identify appropriate populations and develop the necessary infrastructure to perform Phase 3 trials.

## OVERCOMING OBSTACLES TO VACCINES FOR PATHOGENS OF HIGH PUBLIC HEALTH IMPORTANCE

Scientific, technical, theoretical, and political obstacles have hampered the development of several vaccines against diseases of high public health importance. Two such examples, malaria and tuberculosis, are caused by highly evolved microbes that have multiple and complex interactions with their host. Expanding knowledge of the host-pathogen relationship and the genetic organization of those pathogens has resulted in renewed enthusiasm that these microbes, once thought to be intractable to vaccine development, are now amenable.<sup>(3,4,5)</sup> In the United States, other equally important pathogens, previously intractable to vaccine development, have been identified as targets for renewed efforts. Three of the seven selected as highly favorable for vaccine development in a recent Institute of Medicine (IOM) report are public health problems in this country: maternal immunizations against group B streptococcus because of the mode of potential delivery; cytomegalovirus (CMV) because of reactivation and immune evasion potential; and *S. pneumoniae* because of adaptive variability.<sup>(6)</sup> Globally, the World Health Organization (WHO) report on Infectious Disease prioritized six areas of global health importance.<sup>(7)</sup> In addition to tuberculosis and malaria, WHO cited acute respiratory pathogens (pneumonia and influenza), diarrheal diseases, measles, and HIV as targets for vaccine development.

### Goals

- Re-address vaccine development strategies for diseases of greatest health importance using the expanded knowledge gained by novel technologies and microbial pathogenesis.
- Pursue alternative strategies and address existing barriers, such as modes of vaccine delivery, immunopotential, and reactivation, in diseases of high global health importance.
- Pursue programs in neglected areas of national and international needs.

### Opportunities and Plans

A strong program to expand vaccine development capability and opportunities in infectious diseases research will continue to be a component of the NIAID approach. NIAID plans to expand the number of vaccine candidates by:

#### **Federal Malaria Vaccine Coordinating Committee**

NIAID actively collaborates with agencies and organizations interested in developing a malaria vaccine. On the national level, the Institute participates in the Federal Malaria Vaccine Coordinating Committee, an ad hoc group composed of representatives from government agencies engaged in malaria vaccine research. The committee's goal is to ensure the efficient use of federal funds, while expediting the production and testing of vaccine candidates. Internationally, NIAID works closely with the World Health Organization, the Wellcome Trust, and additional organizations supporting malaria research. Recently, under the auspices of the Multilateral Initiative on Malaria, NIAID helped to increase the capacity of African institutions to conduct malaria research and prepare trials for vaccine candidates.

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## NIAID: Planning for the 21<sup>st</sup> Century

- Identifying and evaluating potential antigenic components using comparative sequencing approaches that exploit advances in functional genomics.
- Encouraging structural and chemical definition of potential non-protein antigens, such as polysaccharides and lipids.
- Targeting vaccine development to protect individuals most at risk, including those with impaired, developing, and senescent immune systems.
- Manipulating immune response to enhance vaccine effectiveness through use of adjuvants, cytokines, and other immune modulators.
- Using patient/volunteer cohorts and relevant animal models to identify in complex organisms antibody responses, cytotoxic T lymphocyte responses, and protein/peptide recognition associated with clinical disease progression and protection.
- Maximizing expression of DNA vaccines through identification of suppressor and hyperexpression sequences.
- Developing animal model systems that identify immune responses predictive of human immune response to vaccines.
- Rapidly developing and evaluating candidate vaccines in the clinic, including capsular polysaccharide vaccines for group B streptococcus; polysaccharide conjugate vaccines for *S. pneumoniae*; live, attenuated CMV vaccines and CMV envelope glycoproteins; and protein/polypeptides/DNA from infective, blood, and sexual stages of the malaria parasite.
- Continuing to emphasize other pathogens identified by WHO and the IOM as high-priority global health needs, such as influenza virus, *Mycobacterium tuberculosis*, pathogenic *Escherichia coli*, *Helicobacter pylori*, *Shigella dysenteriae*, *Salmonella typhi*, *Vibrio cholerae*, respiratory syncytial virus, and group A streptococcus.
- Expanding evaluation of alternative strategies for vaccine delivery, including transdermal, mucosal, and edible vaccines.
- Producing pilot lots of candidate vaccines.
- Evaluating candidate vaccines in carefully conducted Phase 1, 2, and 3 trials.

### NEWLY IDENTIFIED AREAS OF VACCINE NEED

The traditional aim of vaccines in public health is to prevent infectious diseases. Expanding the scientific base for developing therapeutic vaccines for chronic diseases and opportunities to improve health through vaccines against non-traditional health targets are important components

of the NIAID plan. NIAID intends to identify and develop vaccine approaches that extend the traditional role of prevention against infectious diseases. To be successful, scientific opportunity and public health need to merge in three areas: 1) management of chronic diseases of infectious and non-infectious origin; 2) control of autoimmune diseases through tolerogenic and non-tolerogenic approaches; and 3) special circumstances, such as the development of vaccines against potential bioterrorism agents.

## **Goal**

- Explore opportunities for vaccine development in less traditional areas, including therapeutic vaccines for the management of chronic diseases; vaccines for the control of autoimmune diseases;<sup>(8)</sup> and vaccines for special circumstances of public health concern, such as bioterrorism.

## **Opportunities and Plans**

### *Chronic Diseases*

Microbial pathogens not previously associated with chronic illnesses (HCV, human papillomavirus, *H. pylori*) are being recognized now because of new capabilities to detect and associate these agents in well-characterized populations. As technological developments continue, the ability to associate infections as critical or causal cofactors in chronic diseases is expanding. The possible causal relationships between microbial pathogens and noncommunicable or chronic diseases (atherosclerosis, Crohn's disease, neuropsychiatric disorders such as schizophrenia, Alzheimer's disease, arthritis, and multiple sclerosis) present opportunities for the application of newly developing technologies.<sup>(9,10)</sup> In addition to the potential for use of pathogen-specific vaccines to manage these diseases, opportunities to modify the innate immune response in chronic diseases by using non-pathogen specific vaccine approaches remains an intriguing possibility.

NIAID, in conjunction with other NIH Institutes, will:

- Focus therapeutic vaccine development strategies on hepatitis B and C, *H. pylori*, and *Chlamydia trachomatis*.
- Explore etiologic bases of chronic diseases. Where evidence suggests an infectious cause of such diseases, NIAID will prioritize efforts to focus on the development and testing of vaccines for their prevention or treatment. (Also see the sections of this Plan on Immune-Mediated Diseases and on Emerging Infectious Diseases and Global Health).
- Evaluate immunologic responses in the context of chronic infections.
- Target vaccine development beyond infectious pathogens.

*Autoimmune Diseases*

Vaccine development for the prevention and treatment of autoimmune diseases has recently been identified as an area of increased importance.<sup>(6,8)</sup> Currently, tolerogenic approaches that selectively modulate the immune response can treat or prevent certain autoimmune diseases in animal models, and clinical trials of tolerance induction agents for prevention and treatment are ongoing in humans. NIAID's recently developed Autoimmunity Network will provide added opportunities to apply genomic approaches to better define the immunologic characteristics of autoimmune populations. In turn, this may allow for the rational development of antigenic specific and non-specific vaccine approaches.

NIAID plans to:

- Begin defining populations (e.g., lupus, scleroderma) where therapeutic and preventative vaccine approaches can be explored, using genomic technologies.
- Explore induction pathways for oral tolerance and systemic tolerance.
- Develop antigen specific (cytokines/anti-cytokines) and antigen non-specific (adjuvant-based) vaccine approaches.

*Bioterrorism*

Vaccines may need to be developed for unique circumstances. The threat of bioterrorism is one contemporary example. Protecting the population from a terrorist attack will require vaccines to be fast acting, easy to deliver, and safe for individuals with varying immune states. The U.S. government has developed a coordinated plan of action involving several agencies to address the threat of bioterrorism in civilian populations. One stated goal is to develop vaccines effective against many of the infectious agents considered candidates for use as bioterrorist threats, including smallpox and other orthopox viruses, anthrax, brucellosis, plague, Q fever, tularemia, viral encephalitides, viral hemorrhagic fevers, and enterotoxigenic pathogens.

NIAID plans to focus efforts on basic and developmental vaccine research needs, including:

- Identifying epitopes that stimulate effective immune responses and that may serve as potential vaccine antigens.
- Evaluating cassette vector systems for the rapid creation of new microbial vaccines.
- Developing vaccines and/or immunization strategies that induce a rapid, protective immune response.
- Developing vaccines that target a generalized response to the innate immune system.

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## ***NIAID: Planning for the 21<sup>st</sup> Century***

- Developing new and improved vaccine adjuvants and cytokines for enhanced immune response and selective immune targeting.
- Evaluating novel vaccine delivery systems (such as oral, nasal, or edible vaccine delivery systems) for optimization of mass public immunization.
- Evaluating passive delivery approaches.
- Evaluating combination (passive and active) delivery approaches.
- Evaluating candidate vaccines in Phase 1 and 2 trials.
- Investigating mechanisms of pathogenesis.
- Evaluating passive immunity and the combination of passive and active immunity.
- Developing model systems as correlates of protection.
- Enhancing relationships with industry, the Department of Defense, the Centers for Disease Control and Prevention, and the U.S. Department of Agriculture.

### **REFERENCED PUBLICATIONS**

1. [The Jordan Report: Accelerated Development of Vaccines, 1998](#)
2. Expert Panel on Basic Immunology of Vaccines, June 1998
3. Blueprint for Tuberculosis Vaccine Development, 1998
4. Vaccines Against Malaria: Hope in a Gathering Storm, Institute of Medicine, 1996
5. [Blue Ribbon Panel on Malaria Vaccine Development, 1997](#)
6. Vaccines for the 21<sup>st</sup> Century, Institute of Medicine, 1999
7. Infectious Diseases: Prioritization for Global Health, World Health Organization, 1999
8. NIAID Workshop on Vaccines for Autoimmune Diseases, 1998
9. Emerging Issues in Microbial Infections and Cardiovascular Diseases, 1998
10. [Crohn's Disease - Is There a Microbial Etiology? Recommendations for a Research Agenda, 1998](#)

### **OTHER RESEARCH PROGRAM PUBLICATIONS**

- [Task Force on Safer Childhood Vaccines, 1999](#)
- Report of the Special Joint DMID and DAIT Subcommittees Session on the Immunological Basis of Vaccine Adjuvants, 1999
- U.S. National Vaccine Plan, 1994
- International Meeting on Nucleic Acid Vaccines for the Prevention of Infectious Diseases. Vaccine 1997;15:8

## **SELECTED CROSSCUTTING ELEMENTS**

Underpinning the four cornerstones of the strategic plan – immune-mediated diseases, AIDS, emerging infectious diseases and global health, and vaccines – are crosscutting needs to develop new technologies, foster application of findings, train investigators, and to interrelate with the Institute's stakeholders.

- [Infrastructure for Technology Development](#). Mining genomic and other research information for its utility in diagnosis, prevention, and treatment, and capitalizing on advances in bioinformatics, imaging, and other technologies will require investment in programs, centers, and other mechanisms that support access to technology and technology development.
- [Translation of Research](#). Ensuring that the nation's investment in biomedical research benefits the public through application in health care is a constant focus of attention. Research planning, applied research, and technology transfer are the means used to carry out this goal.
- [Research Training and Career Development](#). Training the next generation of investigators is an ongoing responsibility. More than ever, tomorrow's health research scientists must be prepared in multidisciplinary fields and be able to quickly apply emerging disciplines to current research questions. Training priorities include expanding opportunities for underrepresented minority investigators.
- [Outreach](#). An active and steady effort to convey the results of research programs to health professionals and the public and to obtain input and advice from the community is essential to the mission of NIAID.

## **INFRASTRUCTURE FOR TECHNOLOGY DEVELOPMENT**

Many of the opportunities and plans detailed in the cornerstones are based on new insights and approaches made possible by DNA sequence information and the capability to manipulate that information with complex computational systems. Such genomic technologies are to bioscience today what particle accelerators were to physics in the mid-20th century. By revolutionizing approaches to pathogenesis, microbial physiology, and epidemiology of infectious diseases, and by radically advancing the understanding of immune activation and regulation, genomic research will markedly accelerate the development of new diagnostic, treatment, and prevention strategies.

Other technologies have had a profound impact on immunology and infectious disease research as well. From computer-assisted means to visualize molecules in three-dimensions to modeling complex interactions, technology is not only accelerating drug development, but also creating the capacity to develop more precise and effective antimicrobial agents, vaccines, and therapeutics for modulating immune responses for diseases such as autoimmune disorders and immunodeficiencies. The emerging field of pharmacogenomics promises to combine knowledge of individual genetic makeup with drug action to increase the efficacy of therapeutics while minimizing side effects.

Realizing the potential of these rapidly evolving technologies, and others yet to be developed, will entail significant investment in infrastructure.

## **Goal**

- Establish the infrastructure to support the development and use of new technologies in immunology and microbiology.

## **Opportunities and Plans**

### *Genomics Centers*

NIAID plans to build on existing capabilities, such as large-scale DNA sequencing, cDNA cloning and expression, and PCR-based techniques, to promote the use of multi-platform, high-throughput genomics in both basic and clinical research. Newly developed genomics technologies will provide tools to identify host-susceptibility genes, characterize patterns of gene expression in response to infection and immune-mediated disease, and identify putative infectious agents associated with chronic diseases. Complementary microbial genomics centers will develop pathogen-specific resources for studies of gene expression, structure, and function in whole microbial genomes and organisms (see [Report of the Blue Ribbon Panel on Microbial Genomics](#), 1999).

- Use of oligonucleotide and cDNA microarrays produced both commercially and in-house for gene and single nucleotide polymorphism discovery and profiling of host gene expression.
- Development, utilization, and distribution to investigators of array-based technologies for studies of differential gene expression in microbes and for molecular epidemiology studies requiring pathogen genotyping.
- Development of new high-throughput tools for protein analysis (proteomics) to assess levels and differential expression of proteins and to correlate gene and protein expression.
- Development of relational databases and new bioinformatics algorithms to store, display, and query the large amounts of genomic, genetic, phenotypic, and clinical data, including gene and protein expression profiles and genetic polymorphisms. Such bioinformatics tools will generate testable hypotheses that lead, for example, to predictors of normal and deleterious immune responses, pathogen virulence factors, drug targets, and mechanisms of drug resistance, and clinical and immunologic responses to interventions.
- Distribution of genomics data and computational tools to the scientific community via the Internet within a reasonable time of discovery.



*Sample Acquisition and Distribution Resource Centers*

NIAID expects to build on existing infrastructure to establish centers that concentrate on collecting and banking pathogen isolates, host tissue, and cell lines for distribution. These centers will include the use of new technologies, such as laser capture microdissection, to ensure homogeneity of samples (isolated microorganisms, single cells or tissues) for other applications, such as genomic or proteomic analyses. Integrated databases will provide field and clinical information with each sample. By correlating genomic information with isolate-specific data, these centers will create synergy with the genomics centers.

*New Technologies Infrastructure and Support*

NIAID intends to build on existing programs to support the development of new technologies and their dissemination to the microbiology, immunology, and infectious disease research communities. Technology development will depend on advances in both academic and industrial research. Partnerships with the biotechnology industry will be sought to obtain access to technologies developed in the private sector and to enhance the transition of new technologies to the field. Areas of current and expanding interest include:

- **Cell-Based Assays.** Support of new instrumentation in multi-parameter FACS and MHC-tetramers. NIAID has established an NIAID [Tetramer Facility](#) to produce custom-soluble MHC Class I/peptide tetramer reagents free of charge to approved investigators.
- **New Imaging Technologies.** Support of new technologies for non-invasive, real-time imaging of immune responses through the adaptation or development of new modalities for high-resolution imaging. In FY 1999, NIAID issued the Request for Applications, "[New Imaging Technologies for Autoimmune Diseases](#)," to promote development in this area.
- **Innovative Development of Animal Models.** Support of improvements in mouse genetic technologies, such as generation of embryonic stem cell lines for rapid production of genetically altered mice, or to perform large-scale mutant generation and phenotyping to identify immune-response or immune-mediated disease genes.
- **Innovative Microbial Technologies.** Support of whole-pathogen, high-throughput methods to study gene function, for example, genome-wide technologies for "bar-coding" all genes.

**TRANSLATION OF RESEARCH**

Every NIAID research program aims to improve health. Even the most esoteric investigation is undertaken with the hope that, in combination with other studies, it will provide insight to improve diagnosis, treatment, or prevention. Yet the path from basic research to health care is a long one, involving many steps and considerable interaction with other organizations. To ensure that the benefits of basic research are realized, NIAID initiates research-planning activities, supports and conducts applied research, and undertakes various technology transfer efforts.

## **Goal**

- Facilitate the movement of fundamental discoveries toward the development of new and improved diagnostics, drugs, and vaccines.

## **Opportunities and Plans**

### *Research Planning*

Sometimes the course required to address a disease problem is clear. More often, an iterative planning process is required to chart and re-chart courses through myriad newly arising questions. In those instances, NIAID often convenes workshops, conferences, or other meetings to help researchers and other stakeholders identify the most important research goals (what basic questions remain to be addressed, what research tools and techniques need to be developed or refined, what concepts are ready for clinical trials). A few recent examples of NIAID planning activities include:

- NIAID Extramural Transplantation Research Program Review
- Project 2000: Research Agenda for Multicenter AIDS Clinical Trials
- [NIAID Research Agenda for Emerging Infectious Diseases](#)
- Consultation on the Emergence of Drug Resistance in *Staphylococcus aureus*
- [Blue Ribbon Panel on Malaria Vaccine Development](#)
- Blueprint for Tuberculosis Vaccine Development
- [Task Force on Safer Childhood Vaccines](#)

Sometimes the process and plan are sufficient to guide research toward application, or back to basic questions that must first be answered. When solving the problem requires new initiative, NIAID will solicit applications to address it through program announcements (PAs), requests for applications (RFAs), or requests for proposals (RFPs). Recently, for example, NIAID issued an RFP to generate animal models of hepatitis C virus (HCV) infection, which was articulated as a high priority by an NIH working group that developed a strategic plan for progress against HCV.

### *Applied Research*

Applied research provides a two-way bridge between basic laboratory findings and their application in clinical, industrial, or other settings. The roles of government and industry in the process are somewhat fluid. Cost of development, likelihood of product approval by the Food and Drug Administration (FDA), and profit from product sales (market size) all influence when and whether private industry takes over development of a concept. In research on rare diseases, for which there are small product markets, and for innovative, financially risky research, government may extend fairly far into the development phases. Government will also take a

more active role in research development when the threat to public health justifies a no-holds-barred attack on a disease.

Support of research along the full investigative spectrum, in part, drives the array of research support mechanisms NIAID uses. In extramural laboratories, for example, when transitional and applied research requires shared resources, and/or a cross-disciplinary research team, program project and center grants (P01, P30, P50) can facilitate the necessary linkages. Cooperative Agreements (U01, U19), which entail substantial involvement of NIAID program staff, are also often used for applied research. Such mechanisms support the National Cooperative Inner-City Asthma Study, the STD Cooperative Research Centers, and the Hepatitis C Cooperative Research Centers.

Special mechanisms also help NIAID intramural scientists advance concepts for development. The NIH Clinical Center provides medical facilities and staff to support clinical trials, and Cooperative Research and Development Agreements (CRADAs) define the scope and terms of collaboration, including the sharing of research and staffing costs, for partnerships between intramural or extramural scientists and industry.

NIAID supports and engages in a variety of activities that directly promote applied research.

- *Clinical Trials.* NIAID supports, conducts, and collaborates on several clinical trials, such as the Diabetes Prevention Trial, the Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation, and many others. In addition, NIAID supports infrastructure that facilitates clinical trials, for example:
  - *Clinical Trial Networks.* Often, a single institution will lack the critical mass of physician-investigators and patients needed to carry out a clinical trial. Clinical trial networks create the necessary infrastructure for cooperation and structured communication among investigators who are conducting related trials. NIAID-supported clinical trial networks include the Adult and Pediatric AIDS Clinical Trial Group, the HIV Network for Prevention Trials, the STD Clinical Trials Unit, the Mycoses Study Group, the Collaborative Antiviral Study Group, and the Vaccine and Treatment Evaluation Units.
  - *Vaccine Production Contracts.* NIAID contracts for vaccine production help meet the need for pilot vaccine lots of vaccines for use in clinical trials.
- *Repositories and Exchange Programs.* Animals often are needed for pre-clinical research because they provide models for the study of human disease. NIAID's Transgenic and Gene-Targeted Mice Repository and the Gene Knockout/Transgenic Mice Exchange Program help meet the need for unique lines of mice.
- *Regulatory Support Capability.* FDA approval is the final step in moving research from the laboratory bench to doctor's office. NIAID staff assists both extramural and intramural scientists through the FDA approval process for drugs, biologicals, and devices, by facilitating and preparing investigational new drug applications.

NIAID will continue to seek and implement mechanisms to promote applied research on immunologic and infectious diseases.

### *Technology Transfer*

Technologies or inventions developed in government-supported laboratories usually must be "transferred" to the private sector for final testing and marketing. The transfer of federally supported technology is governed and encouraged by a set of laws that aim to promote economic development, enhance U.S. competitiveness, and benefit the public by encouraging commercialization of technologies industry might otherwise neglect for lack of incentive.

Federal technology transfer laws generally allow government laboratories and the recipients of government funding to patent (retain title to) and license their inventions. Patents provide the right to exclude others from making, using, or selling a new invention for the life of the patent. In return, the patent holder discloses the patented information in public documents. Parties interested in utilizing patented technologies obtain the right to do so by entering into a licensing agreement with the patent owner. Because companies often will not invest in further research and development of new drugs and vaccines without some promise of product exclusivity, many commercialization licenses are exclusive.

In FY99, the most recent year for which a complete record is available, NIAID had 263 active patent properties and 278 active licenses based on inventions stemming from the creativity of intramural scientists. NIAID-supported, university-based scientists have a similarly remarkable record of technology transfer activity. With assistance from the NIAID Office of Technology Development, NIAID intramural and extramural divisions use a variety of technology transfer mechanisms besides patents and licenses. The FY98 activity with these other mechanisms was significant:

- Material Transfer Agreements (1184)
- Drug Screening Agreements (68)
- Cooperative Research and Development Agreements (CRADAs) and Materials CRADAs (74)
- Clinical Trial Agreements (40)
- Confidential Disclosure Agreements (15)

Particularly notable NIAID technology transfer successes include:

- *Synagis*. FDA approved MedImmune's Synagis, a humanized mouse monoclonal antibody used to prevent respiratory syncytial virus, which causes a serious lung infection in high-risk infants and children. Jointly invented by NIAID and MedImmune scientists, and licensed by MedImmune, Synagis is expected to prevent life-threatening diseases that hospitalize some 90,000 U.S. children annually.

- *Havrix*. A CRADA between NIAID's intramural Laboratory of Infectious Diseases and SmithKline Beechem allowed successful development of Havrix, a vaccine against the hepatitis A virus, which causes the most widespread of viral hepatitis diseases and is endemic in children in the developing world. Licensed by SmithKline, Havrix has been on the market for several years.

NIAID will sustain its vigorous technology transfer activities.

## **RESEARCH TRAINING AND CAREER DEVELOPMENT**

Intellectual talent propels the research enterprise and must be sustained not only to replace retiring investigators, but also to reflect the changing needs of science. From emerging infectious diseases to geriatric immunology, developing fields of science require personnel with new and specialized training. In addition, NIAID is committed to help improve the representation of minorities in research.

### **Goal**

- Ensure that a sufficient number of talented investigators from diverse backgrounds enter immunology and infectious diseases research, and the subfields therein, so shortages of top scientists do not impede basic research or the translation of science advances into medical practice.

### **Opportunities and Plans**

#### *Basic Research*

Through its extramural programs, NIAID will continue to support basic research training using the NIH National Research Service Award (NRSA). NIAID will fund NRSA institutional training grants (T32s) and postdoctoral fellowships (F32s and F33s). In addition, training in basic research will continue under the research career development mechanisms:

- The Research Scholar Development Award (K22), a transition award to support postdoctoral trainees as they move into academic careers.
- The Independent Scientist Award (K02), which supports newly independent scientists during a period of intense research focus.

While these mechanisms cover a broad spectrum of fields, support is targeted to specified shortage areas as needs require.

DIR will continue to use a variety of appointment mechanisms, including the Intramural Research Training Award and various fellowships, to enable postdoctoral basic and clinical scientists to train in NIAID's intramural laboratories.

### *Clinical Research*

Efforts to ensure a robust cadre of clinical investigators will continue to be a priority for NIAID. Building on the Clinical Investigator Award (K08), a mechanism to support extramural medical scientists as they become independent investigators, NIAID recently implemented additional programs designed to increase the number of young scientists interested in patient-oriented research:

- The Mentored Patient-Oriented Research Award (K23) supports young investigators conducting patient-oriented research in their area of medical specialty training.
- The Mid-Career Investigator in Patient-Oriented Research Award (K24) supports physicians who conduct patient-oriented research and the mentoring of clinical investigators.
- The Institutional Curriculum Award (K30) provides support to institutions for the conduct of multidisciplinary didactic training of clinical investigators.

Ethical considerations in clinical research are increasingly complex. NIAID not only participates in, but also administers on behalf of NIH, the following training programs:

- The Short-Term Courses in Research Ethics (T15) award supports the development and conduct of courses that address the ethical, legal, and social implications of research, especially related to human participants.
- Mentored Scientists Development Awards in Research Ethics (K01) supports training of health professionals in research involving human participants.

A variety of appointments will continue to be available to intramural researchers in the Combined Clinical and Research Pathway through programs such as the Clinical Associate Program, Staff Fellowships, and Intramural Research Training Awards.

### *Minority Research Programs*

As long as some minorities are underrepresented among immunology and infectious disease researchers, training members of those communities will be an NIAID priority. Accordingly, NIAID will continue to actively participate in NIH-wide minority research and training programs, such as the National Research Service Award, Individual Minority Predoctoral Fellowship (F31), Minority Biomedical Research Support (S06, S11, S14), Research Supplements for Underrepresented Minorities, and Research Centers in Minority Institutions.

In addition, NIAID will continue to strive for greater representation of minority scientists in biomedical research by providing its own programs. Through the extramural divisions NIAID will provide:

- Enhancement Awards for Underrepresented Minority Researchers. funded research grants for young minority scientists who are mentored by an established investigator in a specific field.
- Howard University Program at the Sexually Transmitted Diseases Cooperative Research Centers. A research training grant (T35) that enables second-year medical students to engage in a 10-week research experience. NIAID plans to model additional programs at minority institutions on the Howard University program.
- Minority AIDS Training Programs. Through the Adult and Pediatric AIDS Clinical Trials Groups, NIAID indirectly supports fellowships for individuals with the potential to conduct clinical research in various aspects of AIDS.

Through DIR, NIAID will provide:

- A program for underrepresented minorities who qualify for postdoctoral, predoctoral, post-baccalaureate, technical, or student Intramural Research Training Awards.
- The Mali Training Program, a student exchange program with the Malaria Research and Training Center in Bamako, Mali. The program facilitates training of underrepresented minority students pursuing advanced degrees in medicine or science in tropical medicine, specifically malaria.

Through the DEA Office of Special Populations and Research Training, NIAID will provide:

- Introduction to Biomedical Research Program, which exposes outstanding minority students at the mid-baccalaureate level to career opportunities in biomedical research through a program of scientific seminars and one-on-one interactions with intramural scientific staff.
- Bridging the Career Gap, a two-day training workshop for underrepresented scientists to provide information on applying for research project grants and opportunities in biomedical research. The workshop also provides the occasion to meet with NIAID intramural and extramural scientific staff.

### *Multidisciplinary Research*

Much of the biomedical science with the most promise for application in health care joins two or more scientific disciplines. Bioinformatics is the most dramatic example, but many melded fields, from neuroimmunology to pharmacogenetics, are remarkably fertile grounds for profound new discoveries. NIAID will continue to evolve its training programs to support such new areas. One example, the Mentored Quantitative Research Career Development Award (K25), provides support to individuals with quantitative science backgrounds who want to apply their expertise to biomedical research.

### *Pre-College Science Education*

In addition to support for training on the post-baccalaureate and postdoctoral levels, the Institute recognizes the importance of engaging the interest of precollege students. As part of the initiative, "Teachers and the NIH: Partners in Science Education," NIAID developed a high-school curriculum supplement that introduces students to the process of scientific discovery in

emerging and re-emerging infectious diseases. NIAID will continue to support activities that interest young people in science.

### **OUTREACH**

The full benefit of NIAID research can be realized only when new knowledge is disseminated not only to other scientists, but also to health care providers and the public. Also, the interests and concerns of the public and other stakeholders must be integrated in the research planning process. NIAID is committed to executing a strong public liaison function in both respects.

### **Goal**

- Promote and sustain interaction with health care professionals and the public through proactive communication of research results, and genuine solicitation and serious consideration of input.

### **Opportunities and Plans**

Although the focal point for outreach in NIAID is the Office of Communications and Public Liaison (OCPL), regular contact with stakeholders of the Institute is a trans-NIAID goal. In order to exchange ideas with constituents, NIAID will continue to initiate and sustain activities including:

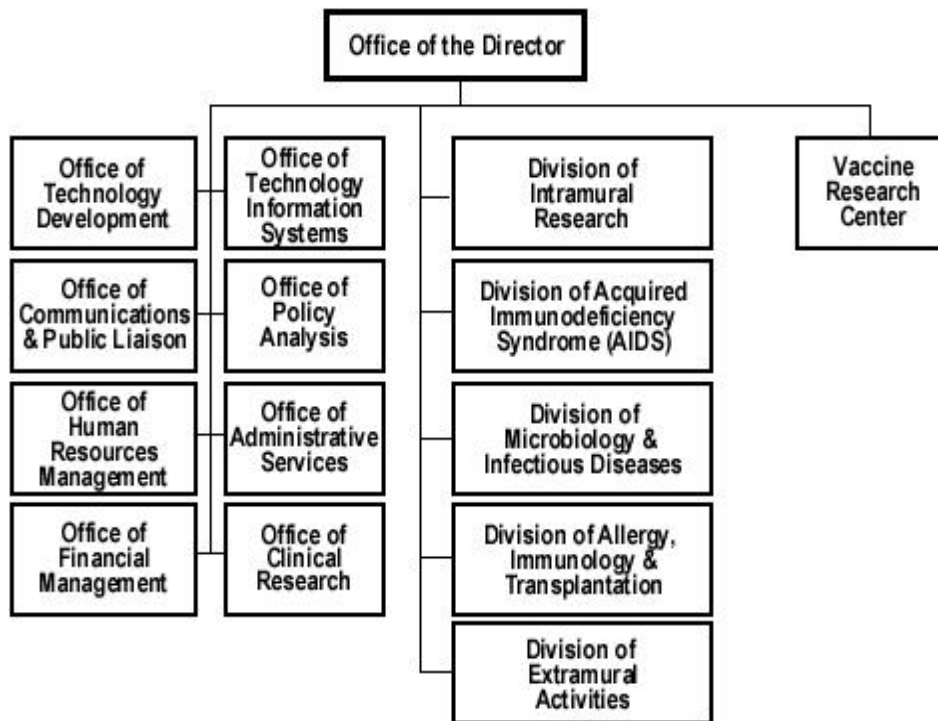
- Periodic meetings with the NIAID Director and representatives of lay groups, such as the American Lung Association and the Juvenile Diabetes Foundation.
- OCPL programs and products that disseminate research result via production of print and audiovisual materials, exhibits, and NIAID's searchable Web site.
- Contributions to the NIH Spanish-language newsletter.
- Meetings that involve the lay community in information dissemination, for example:
  - In April 1999, the Division of Allergy, Immunology, and Transplantation co-sponsored a meeting about new therapies for autoimmune diseases with the American Autoimmune and Related Diseases Association. The program addressed both scientific and non-scientific attendees.



- In 1997, when disconcerting findings about tumors in the offspring of mice given high daily doses of AZT came to light, NIH convened an independent panel to review all relevant data, summarize what was known, and formulate recommendations for future research. Because HIV-infected women and their health care providers were an important target for dissemination of this information, HIV-infected women were included in the panel (see NIAID news release [Reassuring Findings About Infants Exposed to Zidovudine.](#) January 12, 1999).
- Computerized databases such as the AIDS Clinical Trials Information Service (ACTIS) for information about clinical trials.
- Outreach of staff to the local community such as visits of staff from the Sexually Transmitted Diseases (STD) Branch to high schools and churches to educate young people about the causes and consequences of STDs, the epidemiology of the diseases, and prevention strategies.

## APPENDICES

### NATIONAL INSTITUTE OF ALLERGY & INFECTIOUS DISEASES



## **NIAID Council Members**

Five new members joined Council in November 1999. NIAID welcomes **William R. Jacobs, Richard A. Koup, John C. Martin, Magdalene So, and Thelma King Thiel.**

**Jorge L. Benach, Ph.D.,** is professor of microbiology and pathology at the State University of New York at Stony Brook where he is also director of the Infectious Diseases Institute of the Center for Molecular Medicine. A codiscoverer of the etiologic agent of Lyme disease, his research interests have centered on the pathogenesis of spirochetal and other tick-borne infections. Dr. Benach has served on Public Health Service advisory committees, including two NIH study sections, and on the editorial boards of several journals.

**Kim Bottomly, Ph.D.,** is professor of immunobiology and dermatology, Yale University School of Medicine. Dr. Bottomly was a member of the Immunobiology Study Section and has served on several committees of the American Association of Immunologists. Her research focuses on the factors that regulate CD4<sup>+</sup> T-cell differentiation and function. Dr. Bottomly's recent studies are building on her research findings in this area to broaden understanding of the role of CD4<sup>+</sup> T cells in the pathogenesis of asthma.

**Robert B. Couch, M.D.,** is professor and chairman, Department of Microbiology and Immunology, and professor of medicine, Baylor College of Medicine. He has served on many advisory committees, including an NIH study section, NIAID Board of Scientific Counselors, National Vaccine Advisory Committee, and the FDA Vaccines and Related Biological Products Advisory Committee. Dr. Couch was an associate editor of research journals and a microbiology text book. His research has focused on acute respiratory diseases, particularly influenza and rhinoviruses, and vaccine development.

**Lawrence Deyton, M.S.P.H., M.D.,** is director of HIV/AIDS services and research for the Department of Veterans Affairs. Dr. Deyton's interests are HIV clinical research and strategies of HIV treatment. He served in several positions in NIAID between 1987 and 1998: acting director of Division of Extramural Activities, chief of the HIV Research Branch, and chief of the Community Clinical Research Branch in DAIDS and was a fellow in infectious diseases in NIAID's Laboratory of Immunoregulation.

**Lt. Col. Theodore M. Freeman, M.D.,** is chairman, Department of Allergy/Immunology, Wilford Hall Medical Center, Lackland Air Force Base, San Antonio, Texas. A member of the U.S. Air Force, he is program director for the Allergy/Immunology Fellowship Program and Clinical Laboratory Immunology Fellowship Program and medical co-director of the Clinical Immunology Laboratory, which includes the transplantation lab section at Wilford Hall Medical Center. His research has focused primarily on environmentally related allergy topics, specifically medical aspects of the imported fire ant.

**Raif S. Geha, M.D.,** is a professor of pediatrics at Harvard Medical School and Chief of Immunology at Children's Hospital, Boston. Dr. Geha's long-standing research interest is in the molecular basis of IgE synthesis and primary immunodeficiencies. His work examines the roles

of CD40 signaling in isotype switching, SLP-76 in the function of hematopoietic cells, the Wiskott Aldrich protein in cytoskeletal reorganization, and skin injury in atopic sensitization.

**Janis V. Giorgi, Ph.D.**, is professor of medicine, UCLA School of Medicine, and director, UCLA Research Core Flow Cytometry Facility, Jonsson Comprehensive Cancer Center, and the Center for AIDS Research. Dr. Giorgi studies AIDS immunology and has published on immunophenotypic and functional alterations of HIV-1 disease. Her research is directed at identifying mechanisms of host protective immunity against viral infection and pathogenesis. She is active in developing clinical immunology, especially applications of flow cytometry in the diagnosis and prognosis of disease.

**Ellen H. Goldberg, Ph.D.**, is president, Santa Fe Institute, and research professor of biology, Department of Microbiology, University of New Mexico School of Medicine, previously serving as chair of microbiology and associate provost of research and dean of graduate studies. Dr. Goldberg has participated on NIH study sections and the National Task Force on the NIH Strategic Plan. She is past chair, Immunology Division, American Society for Microbiology, and fellow of the Academy of Microbiologists. Dr. Goldberg's research focuses on differentiation antigens.

**Barton F. Haynes, M.D.**, is the Frederic M. Hanes professor and chair, Department of Medicine, and director of the Human Vaccine Institute at Duke University. Dr. Haynes studies the biology of the human thymus and is currently exploring ways to reconstitute the immune system in HIV infection. Dr. Haynes also guides an HIV vaccine program to design adjuvants and immunogens to induce protective immune responses to HIV.

**James M. Hughes, M.D.**, is the director of the National Center for Infectious Diseases of the Centers for Disease Control and Prevention. Dr. Hughes has published on many infectious disease topics, including the epidemiology and pathogenesis of enteric diseases and the epidemiology, surveillance, and control of nosocomial and emerging infections.

**Williams R. Jacobs, Jr., Ph.D.**, is professor in the Departments of Microbiology and Immunology and Molecular Genetics at Albert Einstein College of Medicine (AECOM) and investigator in the Howard Hughes Medical Institute. Dr. Jacobs studies mycobacteria and has made significant contributions in identifying the mechanisms of action of the mycobacterial drugs isoniazid and ethionamide as well as novel factors of *M. tuberculosis* required for growth and persistence *in vivo*. He has authored over 75 original publications on mycobacteria and numerous reviews.

**Richard A. Koup, M.D.**, is the Jay P. Sanford professor of infectious diseases and chief, Division of Infectious Diseases, the University of Texas Southwestern Medical Center. Dr. Koup's research interests include the immunopathogenesis of HIV, cellular immunity to HIV, the role of the thymus in immune reconstitution, and co-receptors in HIV entry. Dr. Koup has served on NIH study sections, the NIAID Strategic Plan Task Force, and as a scientific advisor to academic HIV research centers.

**Thomas J. Lawley, M.D.**, is dean and William P. Timmie professor of dermatology, Emory University School of Medicine, as well as vice president of Emory Healthcare and president of Emory Medical Care Foundation. Dr. Lawley is the former chair of dermatology at Emory. His areas of research interest include autoimmune skin diseases, the cell biology of endothelial cells, and regulation of cell adhesion molecules. Dr. Lawley has served on many boards and committees, including NIH study sections.

**Stephan E. Lawton, J.D.**, is a lawyer in a private practice, representing medical specialty organizations, and public health associations. These organizations include the American Academy of Pediatrics, the Infectious Diseases Society of America, the American Cancer Society, and the Endocrine Society. Mr. Lawton has also worked on Capitol Hill developing legislation in health-related areas, and was recently chairman of the PHS Advisory Commission on Childhood Vaccines.

**John C. Martin, Ph.D.**, is the president and chief executive officer of Gilead Sciences, Inc. Previously, he was employed at Bristol-Myers Squibb and at Syntax Corporation where he was the co-inventor of ganciclovir. He is president of the International Society for Antiviral Research and received the Isbell Award of the American Chemical Society for his applications of carbohydrate chemistry to the design of medicinally active nucleosides and nucleotides.

**Marie M. Saint Cyr, M.S.W.**, is the executive director of Iris House, the first and only comprehensive program for women living with HIV/AIDS and their families. She serves as an appointee of Mayor Guiliani as community co-chair of the HIV Planning Council of New York City. She is also chairperson of the board of the National Minority AIDS Council in Washington, D.C., and serves on local advisory boards. Ms. Saint Cyr has been a fervent advocate for people with AIDS and their families since 1984, helping to bring resources to the communities in dire need of help.

**Magdalene So, Ph.D.**, is professor and chair of the Department of Molecular Microbiology and Immunology at the Oregon Health Sciences University. She has served on the Bacteriology and Mycology 1 study section and a number of other NIH panels. She is presently serving on the editorial boards of several scientific journals and as vice chair of the Committee on Conferences of the American Society of Microbiology. Her research focuses on the pathogenic *Neisseriae*, in particular, the genetic, cellular, and biochemical events that mediate bacterial adhesion, entry, and trans-epithelial migration.

**Emily J. Spitzer, J.D.**, is the immediate past chair of research for the Juvenile Diabetes Foundation International. In addition to serving on its International Board of Directors, she has participated in the organization's grant review process for the past seven years and has also served on its Government Relations Committee helping to formulate strategies to encourage more biomedical research not only in the public sector but also in partnership between public and private organizations.

**Thelma King Thiel, R.N., B.A.**, is the founder, voluntary chair, and chief executive officer of the Hepatitis Foundation International. She has served on the National Commission on Digestive Diseases, the National Digestive Diseases Advisory Board, as president and chief operating officer of the American Liver Foundation, and as chair of the Digestive Diseases National

Coalition and is a fervent participant in numerous patient advocacy organizations. Following the loss of an infant son to a rare liver disease 30 years ago, she created a "liver character," developed unique liver wellness and preventive education programs and materials, lectured extensively, published articles, and was featured in a PBS Documentary, *The Visionaries*.

**Emil R. Unanue, M.D.**, is professor of pathology and head, Department of Pathology and the Center for Immunology, Washington University School of Medicine. He has served on NIH advisory committees, most recently the NIAID Board of Scientific Counselors. Dr. Unanue's long-standing interest is the biology and molecular understanding of antigen processing and presentation. His work examines the biochemical basis of peptide presentation by class II histocompatibility molecules, including autologous peptides involved in autoimmune diabetes, and innate immune responses to intracellular pathogenic bacteria.

**Lowell S. Young, M.D.**, is director, Kuzell Institute for Arthritis and Infectious Diseases, and clinical professor of medicine, University of California San Francisco. Dr. Young's research includes basic investigation of bacterial pathogenesis and treatment of opportunistic infections especially in immunocompromised hosts. He is editor of *Antimicrobial Agents and Chemotherapy* and an author of over 300 research papers and book chapters. Dr. Young has received the Langmuir Prize from CDC and Garrod Medal of the British Society for Antimicrobial Chemotherapy.

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**Panel on Immune-Mediated Diseases**

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**Chair**

Hugh McDevitt, M.D.  
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Department of Microbiology and Immunology  
Stanford University School of Medicine

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**Liaison**

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Emil Unanue, M.D.  
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**Rapporteur**

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**Panel on AIDS**

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**Chair**

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**Panel on Emerging Infectious Diseases**

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**Chair**

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**Panel on Vaccines**

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